Pharmacologic Management of ADHD

CHADD Presentation
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• I have no conflicts of interest or disclosures
• I will briefly discuss some off-label use of medications
• * Not a biochemist
• * Just one guy
Outline

- When to start medications?
- “First line” versus “second line” therapy
  - Pros and cons
  - Differences between types
- The decision making process
- Complementary and alternative medication choices
- Frequently Asked Questions
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American Academy of Pediatrics Practice Guidelines

- Children aged 4-5 years
  - Evidence-based parent and teacher behavior therapy
  - Medication (stimulants) if therapy does not help enough
- Children 6-11 years
  - Parent and teacher therapy or/and medications (preferably both)
- Adolescents 12-18 years
  - Medications with or without behavior therapy
- Adults?
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First Line: Stimulants

- Drug family first developed in 1940s
- First line of treatment for ADHD
- Effect size 1.0 compared to second line treatments (0.7)
- Main two classes: methyphenidate (e.g. Ritalin) and mixed amphetamine salts (e.g. Adderall)
- Basically all provide same medication in different packaging
How they work

1. DA or NA is released into the synapse
2. DA or NA reversibly attaches to receptors
3. MPH blocks reabsorption of DA or NA from the synapse

Image credit: ADHD Institute
Pharmacokinetics

Mechanisms of Delivery-- Wax Matrix

- Ritalin SR
- Metadate ER
- Metylin ER
Mechanisms of Delivery--OROS

- Concerta
- Methylphenidate-OROS

Alza’s Osmotic Controlled Release Oral Delivery System (OROS)

Image credit: Medscape
Mechanisms of Delivery--Beads

- Adderall XR
- Focalin XR
- Ritalin LA
- Metadate CD
- Quillivant
Mechanisms of Delivery -- Prodrug

- Vyvanse

Lisdexamfetamine dimesylate

\[
\text{d-amphetamine}
\]
Mechanisms of Delivery--Transdermal

Methylphenidate Transdermal System (MTS, *Daytrana*™): DOT MatrixTM

- Backing
- Drug/Adhesive Mix
- Release Liner

Evenly dispersed methylphenidate blend

Adhesive

Magnified view

Image credit: Medscape
On the horizon:

- Delayed and Extended Release Methylphenidate—Benjorna
  - Taken in evening
  - Begins working in about 8 hours (?)
  - Effects last 8-10 hours (?)

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<table>
<thead>
<tr>
<th>Medication</th>
<th>Formulation</th>
<th>Duration of Action (hrs)</th>
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<tbody>
<tr>
<td>Ritalin IR</td>
<td>Tablet</td>
<td>3-4</td>
</tr>
<tr>
<td>Focalin IR</td>
<td>Tablet</td>
<td>4-6</td>
</tr>
<tr>
<td>Methylphenidate IR</td>
<td>Tablet</td>
<td>3-4</td>
</tr>
<tr>
<td>Metadate ER</td>
<td>Wax matrix</td>
<td>6-8</td>
</tr>
<tr>
<td>Ritalin SR</td>
<td>Wax matrix</td>
<td>4-8</td>
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<tr>
<td>Ritalin LA</td>
<td>Extended release beads</td>
<td>8-10</td>
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<tr>
<td>Quillivant XR</td>
<td>Extended release beads (liquid)</td>
<td>8-12</td>
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<tr>
<td>Focalin XR</td>
<td>Extended release beads</td>
<td>6-10</td>
</tr>
<tr>
<td>Concerta</td>
<td>OROS</td>
<td>10-12</td>
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<tr>
<td>Metadate CD</td>
<td>Extended release beads</td>
<td>8-10</td>
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<tr>
<td>Adderall IR</td>
<td>Tablet</td>
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<tr>
<td>Adderall XR</td>
<td>Extended release beads</td>
<td>8-12</td>
</tr>
<tr>
<td>Vyvanse</td>
<td>Capsule (pro-drug)</td>
<td>10-12</td>
</tr>
<tr>
<td>Daytrana</td>
<td>Patch</td>
<td>10-12</td>
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Combining Stimulants

- Long-acting stimulants can be combined with short-acting stimulants for certain cases (usually older children)
- Short-acting medication designed to simulate an extra $\frac{1}{2}$ dose of the long-acting
- Typically dosed before the long-acting medication wears off
Pros and Cons: Stimulants

Pros
- Effective
- Quick on/off (same day results)
- Easily adjusted
- Easily stopped

Cons
- Work only during daytime/school hours
- Controlled substance
- Abuse/diversion potential
- Side effects
Side effects: Stimulants

- Common
  - Headaches, stomachaches
  - Decreased appetite
  - Sleep problems
  - Emotional lability (as medication wears off)

- Uncommon
  - Hallucinations and psychosis
  - Heart rate or blood pressure increase

- Unclear
  - Increased Tics
  - Increased anxiety
  - Diminished growth (1-3 cm total) versus delayed growth?
  - Heart rhythm problems?
Cardiac Warnings

- Unclear if stimulant medications increase risk of sudden death (conflicting recommendations from the American Academy of Pediatrics, the American Academy of Child and Adolescent Psychiatry, and the American Heart Association)
- Inquire about family history of congenital cardiac disease, hypertrophic cardiomyopathy, and sudden cardiac death (rhythm abnormalities)
- Consider cardiac clearance work-up if concerns on exam or history
Overtreatment

- Over-focused
- Sad
- Tired
- “Like a zombie”
Second Line Treatments

• Alpha-2 Agonist
  • Drug family first developed in 1970s
  • Initially developed as blood pressure medication
  • Benefits on hyperactivity and inattention
  • May cause rebound hypertension if stopped suddenly
  • Guanfacine and clonidine (Tenex, Intuniv, Kapvay, Catapress)

• Atomoxetine (Strattera)
  • Developed in 21st century
  • Selective norepinephrine reuptake inhibitor (SNRI)
Pros and Cons: Second Line Treatments

**Pros**
- “Less” side effects
- Not controlled substances
- Longer coverage throughout day
- Possible additional benefits on other symptoms (tics, aggression, anxiety)

**Cons**
- Longer time to effect
- Less dramatic/obvious results
- Harder to start/stop (e.g. during holidays or weekends)
- Side effects
Side effects: Alpha-2 Agonists

- **Common**
  - Sleepiness
  - Constipation
  - Dry eyes and mouth
- **Uncommon**
  - Irritability
  - Low blood pressure
Side effects: Atomoxetine

- Common
  - Decreased appetite
  - Sleepiness
  - Sexual dysfunction
  - Constipation
  - Dry eyes and mouth
- Uncommon
  - Liver inflammation
  - Suicidal thoughts
  - Heart problems
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Deciding to Try Medications

- Child’s age
- Child’s ADHD symptoms
- Child’s other symptoms (depression, anxiety, learning problems)
- School and home environment
- Parental readiness
Which Medication Is Best?

- Needs for attention during the day
  - How long does he/she go to school?
  - What time is homework?
  - What other demands does the child/family have?
- What are the child’s other symptoms?
- Can the child swallow a pill?
- What has worked for any family members?
  - Side effects differ on drug and even sometimes by manufacturer
  - Pharmacogenomic testing?
- Trial and error
Case Examples

- 5 year old boy attending preschool under an IEP with impulsive and aggressive behaviors inhibiting his learning
  - Short-acting stimulant versus alpha-2 agonist

- 16 year old high school student who also plays baseball in the afternoon
  - Vyvanse +/- Adderall IR in the afternoon
General Treatment Algorithm: First Line

1. Pick a stimulant, any stimulant (covered and available is best) based on length of needs.
   - usually start with long-acting dose unless very young
2. Increase the stimulant to max tolerated dose (can increase after 2-4 days per dose)
   - generally speaking, community clinicians under-dose medication when compared to research clinicians
3. Once optimal dose is achieved, monitor for side effects (every 3 months) and effectiveness via teacher, parent, or self report (at least annually).
   1. Heart rate, blood pressure
   2. Weight and height
   3. Behavioral side effects
Dealing with side effects: stimulants

- Encourage lifestyle modifications
  - Afternoon meltdowns: emotional “cooldown” period in afternoon
  - Sleep problems: Sleep hygiene
  - Low appetite: increased calories
- Take breaks on the weekends and holidays
  - Usually for low appetite
  - No evidence to suggest improvement
- Decrease the dose and add a second line medication
- Add another medication to treat side effects
- Try a different medication
Dealing with failure: stimulants

1. Switch medication to another stimulant (move between classes of stimulants)
   - ~70% of children will respond to first drug, ~70% of initial non-responders respond to second drug

2. If no effective stimulant in 3 tries, move to non-stimulant options
   - Can use stimulant and alpha-2 agonist together
General Treatment Algorithm: Second Line

1. Start at initial dose and maintain for one month.
2. Increase dose gradually to max tolerated dose (over one month).
3. Monitor for side effects (every 3-4 months) and effectiveness via teacher, parent, or self report (at least annually).
Treatment Failure

- Rarely due to lack of any response
- Often failure is driven by side effects
- Consider general health issues (SLEEP)
- Re-consider alternative diagnoses (e.g. Autism Spectrum Disorder, Anxiety, Post-Traumatic Stress Disorder, Learning Disorder, Bipolar Disorder)
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Fish Oil / Omega 3 Fatty Acids

1. Lipids are important for brain health
2. Lipid imbalances are associated with ADHD
3. Lipid levels might be affected by different parameters
4. It’s all in the composition! Higher brain bioavailability for certain lipids compositions
Fish Oil / Omega 3 Fatty Acids

- Mild benefit seen in research studies
- Exact dose and formulation not clear
- Tolerance and compliance is an issue
- Long-term treatment (not immediate results)
- “Prescription strength” available (Vayarin)
Restricted Diets (e.g. Feingold)

• In general, available research on special diets is limited
• Effect sizes/improvements typically small
• Most effects seen in parent-report, not teacher report
• No harm in restricted diet (but requires parent energy and commitment)
Biofeedback

- Some research studies have shown mild improvement
- Not enough long-term studies to demonstrate sustained improvement
- Not enough research to determine dose length or intensity
- Not covered by insurance (can be very costly)
Complementary approaches in general

- Effects are going to be gradual and subtle
- Generally 3 months should be sufficient for a trial
- Use “blinded” reporters
- ABAB withdrawal

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“Won’t he get addicted?”

- Estimate 15-25% of substance abusers have ADHD
- Adults with ADHD twice as likely to be substance abusers
- Substance users with ADHD abuse earlier and more often than those without ADHD
- Self-medication versus complication of disorder
- Stimulant treatment does not increase risk of future substance abuse (and may decrease it)
“Why can’t I just give him coffee?”

- Caffeine may produce similar benefits
- Benefits are generally milder
- Caffeine content varies per cup of coffee
- Dosing and length of effect are difficult to control
- Caffeine has other side effects
“Does he have to take this forever?”

- Brains change over time, but so do expectations and demands
- Adult ADHD rates 4-5% (less than childhood ADHD rates of 5-11%)
- ~50% of children with ADHD will retain the diagnosis as adults (?)
- Rates of adults with ADHD on treatment roughly <50%
- Increased rates of marriage problems, school problems, job difficulties, problems with law, and quality of life
“What if he abuses the medication?”

- Long-acting stimulants generally do not provide the “high” due to delayed release
- It is difficult to adjust the way the medication is taken to increase the rate of absorption (e.g. crushing and snorting)
- Diversion is much more of a concern than abuse
Thank you!