Disclosures

- Research support from CMS and HRSA
- Consultant for Optum
- Book royalty from American Psychiatric Association Publishing

Off-label medication use is discussed in this presentation, and it will be noted where it occurs.
Learning Objectives

• Better differentiate ADHD from other causes of inattention and hyperactivity
• Confidently manage ADHD prescription medication treatment options
• Counsel parents effectively on their non-medication and herbal supplement options

ADHD: What is it Really?

• Per DSM-5 a "neurodevelopmental disorder"
• Pervasive, persistent biologically driven trait of hyperactivity, impulsivity and shortened attention span (relative to age based norms)
  • Has adaptive values: ex. for pushing past fears of new environments or trying new actions
  • Not adaptive for tasks which require sustained and calm attention
    • Modern day class rooms
    • Modern day desk based jobs
The Cause of ADHD?

• Highly heritable
  • 92% concordance in monozygotic twins
• Generally involves some alteration of catecholamine processing in the prefrontal cortex
  • Different linked genes in
    • dopamine transporters
    • serotonin transporters
    • glutamate receptors
    • serotonin receptors
• Prefrontal cortex: inconsistent reports of anatomical and functional differences

Other Causes of ADHD Symptoms

• Anything else which can cause brain dysfunction
  • Substance exposure in utero
  • Brain injury
  • Low birth weight (even in full term infants)
  • Preterm birth
  • Organophosphate pesticides
  • Early environment deprivations
• Dietary causes are minimal or absent (per controlled studies)
  • There are occasional outliers
Diagnosis

- Symptoms before age 12 (DSM-IV was before age 7)
- 6 months minimum duration
- 2 or more settings
- Clinically significant impairment
- Not explained by another disorder
- 6 or more symptoms of inattention, hyperactivity or both
  - For adults, only 5 symptoms are required
  - Rating scales help, but don’t make the diagnosis for you

Inattention: 9 Symptom List

- Lacks attention to detail/careless mistakes
- Difficulty sustaining attention
- Does not seem to listen when spoken to
- Poor follow through
- Difficulty with organization
- Avoids tasks requiring sustained mental effort
- Loses things
- Easily distracted
- Forgetful
Hyperactivity/Impulsivity: 9 Symptom List

• Fidgets
• Difficulty staying in seat
• Runs/climbs excessively (restless in adolescents)
• Difficulty engaging in quiet activities
• “On the go”
• Talks excessively
• Interrupts
• Difficulty awaiting turn
• Blurs out answers before question completed

Other Disorders Which Mimic ADHD

• Anxiety
• Depression
• Learning Disability
• Low cognitive functioning
• Oppositional Defiant Disorder
• Autism Spectrum Disorder
• Substance use disorder
Comorbid Conditions

- ADHD often has a partner disorder
  - ODD (55-85%)
  - Substance abuse (20-40%)
  - Conduct (10-20%)
  - Language or Learning problem (25-35%)
  - Anxiety (33%)
  - Tic disorder (50%)
  - Mood disorders
  - Sleep problems

ADHD Prevalence and Prognosis

- Prevalence 6-9% (2x boys vs girls)
- Many have symptoms persisting into adulthood
  - Up to 90% will still have some symptoms of ADHD
  - Rule of thirds for severity persistence
    - ~2/3 still need med for normal range function in high school
    - ~1/3 still need med for normal range function adulthood
Long-term Consequences of ADHD

- Associated consequences in adults
  - Traffic and other accidents
  - Marital difficulties
  - Unemployment
  - Antisocial and criminal behavior
  - Lower household income

Evaluating ADHD

- A clinical diagnosis, taking into account the whole child and their life circumstance
- No specific testing or imaging is indicated, with two common exceptions
  - IQ testing if low cognitive ability
  - Learning disability testing if low achievement relative to abilities
- Rating scales help elicit symptoms from other informants
  - Multi-site symptoms is a diagnostic requirement
- Comparison to peers
  - Inattention/hyperactivity is typically normal in preschoolers
- Response to stimulants is not unique to ADHD
  - Therapeutic trials do not aide in diagnosis
Work-up

• If other reasons to suspect, could consider more evaluation for
  • Lead
  • Thyroid
  • Seizures
  • Obstructive Sleep Apnea
  • Anemia
  • Trauma
  • Substance abuse
  • Sensory impairment
  • Brain injury
  • Genetic syndrome

Medication side effects may mimic ADHD

• Corticosteroids
• Bronchodilators
• Antihistamines
• Antipsychotics
• Levetiracetam (Keppra)
Treatment Recommendations

• Psychoeducation
  • Help parents and child understand the disorder

• Behavior management training (for caregivers)
  • Rewarding desirable behaviors, non-punitive consequences for negative behaviors
  • Maintain schedule, organize home, set small goals, limit choices, use charts/lists to maintain focus, encourage successful activities, reduce distractions, use calm discipline
    • Many examples like Incredible Years, Parent-Child Interaction Therapy, Positive Parenting Program, Kazdin Method

• Training in skills deficits
  • Coach the child in organization and planning

Treatment Recommendations

• Classroom interventions
  • Homework notebook, extended time for tasks, daily report card, reduced distractions (seat away from window, doors)
  • Frequent breaks, physical movement when possible, tutoring, help with creating organizational system, signal from teacher when off task

  • Classroom interventions are effective in improving achievement scores, but benefits sustained only as long as interventions continued
Medication Options—Three Groups

• Stimulants
  • Methylphenidate
  • Dextroamphetamine
• Alpha 2 agonists
  • Clonidine
  • Guanfacine
• Noradrenergic agents
  • atomoxetine

Stimulants

• All increase extracellular dopamine in striatum and noradrenaline in prefrontal cortex
  • Dextroamphetamine differs by adding some serotonin reuptake inhibition and induces some release of monoamines from presynaptic terminals
• Stimulants can yield protective reductions of these comorbidities
  • Depressive and anxiety disorders
  • Disruptive behavior
  • Family quality of life
  • Repeating a grade
Stimulants

- Most medication trials should start with either methylphenidate or dextroamphetamine
  - Dextroamphetamines FDA approved ≥3 year old
    - Dexedrine, Dextrostat, Adderall, Vyvanse
  - Methylphenidates FDA approved ≥6 year old
    - Ritalin, Methylin, Concerta, Metadate, Focalin
- Similar efficacy
- Side effects sometimes more pronounced with the dextroamphetamines
- Start low, but increase to an adequate dose before moving on
  - Straight up weight based prescribing is not recommended due to variable effectiveness, but
  - Usually see positive results before reaching 1 mg/kg/d methylphenidate or 0.5mg/kg/day dexamphetamine. I would never prescribe more than twice those amounts for safety reasons.

Stimulants—why so popular?

- Most effective medication treatment in child psychiatry
- Immediately effective, no build-up required
- 85% of children with ADHD will respond to one of the stimulant medications
- Generally more clinically effective than the non-medication treatments
- Well done, large scale research support (i.e. MTA study)
Multimodal Treatment of ADHD Study (MTA)

- 600 children, 7-9 yo
- Treatment modes:
  - intensive medication management (methylphenidate tid, other drugs if necessary; algorithmic adjustments; general advice and readings);
  - intensive behavioral treatment alone (parent training; structured teacher consultation; full time summer treatment program; half time classroom behavioral specialist);
  - a combination of both;
  - routine community care (the control group).

The MTA Cooperative Group. A 14-month Randomized Clinical Trial of Treatment Strategies for Attention-Deficit/Hyperactivity Disorder. Arch Gen Psychiatry 1999; 56: 1073-1086.

MTA at 14 months

- Combination treatment and medication management are superior to behavior management and community care.
- Combination treatment is better for certain areas of functioning:
  - oppositional/aggressive symptoms, anxiety symptoms, reading achievement, parent-child relations, and social skills.
- 4% of patients stopped medications due to adverse effects.
- About 1 mg/kg optimal of methylphenidate
MTA at 8 years

- After initial 14 months of treatment, patients returned to community care.
  - No outcome differences between original treatment groups at 8 years
- MTA group as a whole functioned less well than the non-ADHD classmate sample
- Children with behavioral, socio-economic, or intellect advantage or best response to treatment have the best prognosis.

Preschool ADHD Treatment Study (PATS)

- NIMH funded multi-center randomized efficacy trial
- 3-5.5 y.o. with severe ADHD unresponsive to 10 week psychosocial intervention
- 37 out of 279 patient parents said behavioral treatment resulted in satisfactory improvement
PATS

- Outcomes: Stimulants were effective, but
  - lower end doses
    - mean optimal methylphenidate dose 14.2 mg/day or 0.7 mg/kg
  - lower effect sizes
  - higher rates of side effects
    - crabbiness, proneness to crying, irritability

PATS Follow Up

- PATS at 6 years:
  - Persistent ADHD diagnoses—89.9% still meeting diagnostic criteria for ADHD
  - Patients with comorbid ODD or conduct disorder had higher rates of ADHD
  - Girls experienced a more rapid symptom decline (but girls’ baseline symptoms more severe)
  - Hint of positive long-term benefit on parent ratings for those who completed the study

Riddle et al 2013
### Immediate Release Stimulants

<table>
<thead>
<tr>
<th>Name</th>
<th>Duration of Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methylphenidate (Ritalin, Methylin)</td>
<td>3-5 h</td>
</tr>
<tr>
<td>D-methylphenidate (Focalin) 2x mg:mg potency of methylphenidate</td>
<td>3-5 h</td>
</tr>
<tr>
<td>Mixed amphetamine salts (Adderall)</td>
<td>4-6 h</td>
</tr>
<tr>
<td>Dextroamphetamine (Dextrostat, Dexedrine)</td>
<td>4-6 h</td>
</tr>
</tbody>
</table>

### Long Acting Methylphenidates

<table>
<thead>
<tr>
<th>Name</th>
<th>Mode of Delivery</th>
<th>Duration of Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metadate ER/Ritalin SR/Methylin ER</td>
<td>Wax or methylcellulose matrix</td>
<td>4-8 h</td>
</tr>
<tr>
<td>Concerta</td>
<td>22% IR, pump</td>
<td>Up to 12 h</td>
</tr>
<tr>
<td>Metadate CD</td>
<td>30% IR, 70% 3 h later</td>
<td>7-9 h</td>
</tr>
<tr>
<td>Ritalin LA</td>
<td>50% IR, 50% 4 h later</td>
<td>7-9 h</td>
</tr>
<tr>
<td>Focalin XR (remember 2X mg:mg potency)</td>
<td>50% IR, 50% 4 h later</td>
<td>Up to 12 h</td>
</tr>
<tr>
<td>Daytrana patch</td>
<td>Gradual transdermal release</td>
<td>Up to ~4 h after removal</td>
</tr>
<tr>
<td>Cotempla XR-Oral disintegrating tabs</td>
<td>25% IR, 75% XR in microbeads</td>
<td>Up to 12 hours</td>
</tr>
<tr>
<td>Aptensio-SR</td>
<td>Single bead type 40% IR, 60% delayed</td>
<td>7-12h</td>
</tr>
<tr>
<td>Journay PM (8 hour init. release delay)</td>
<td>Double coated beads, double delay</td>
<td>~10 hours after release</td>
</tr>
</tbody>
</table>
Long Acting Amphetamines

<table>
<thead>
<tr>
<th>Name</th>
<th>Mode of Delivery</th>
<th>Duration of Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adderall XR</td>
<td>Capsule MAS 50% IR, 50% 4 h later</td>
<td>8-12 h</td>
</tr>
<tr>
<td>Mydayis</td>
<td>Capsule MAS IR, and two delayed release beads</td>
<td>Up to 12 hr</td>
</tr>
<tr>
<td>Dexedrine spansule</td>
<td>Capsule 50% IR, 50% gradual</td>
<td>10 h</td>
</tr>
<tr>
<td>Vyvanse</td>
<td>Capsule and chewable, lysine cleaved after absorption</td>
<td>10 h</td>
</tr>
<tr>
<td>Adzenys XR-ODT</td>
<td>ODT, Amphetamine 50% IR, 50% XR microbeads</td>
<td>10 h</td>
</tr>
<tr>
<td>Dyanavel</td>
<td>Liquid with IR and XR microbeads</td>
<td>10 h</td>
</tr>
</tbody>
</table>

MAS=mixed amphetamine salts  
ODT=oral disintegrating tablet

Stimulant Side Effects

- Most common problems:
  - Appetite decrease
  - Insomnia
  - Headaches
  - Stomachache
  - Dry mouth
  - Emotional lability/aggression
  - Growth velocity decrease weight and height, maybe up to 1 inch
    - Growth charts are really helpful
- Options: decrease dose, switch, or augment (eg, add clonidine or melatonin for sleep)
Cardiac Concerns

- Commonly yield a small increase in BP and Pulse
  - Need to check after initiation, to ensure no outlier response
- ADHD medications overall do not appear to increase the risk of serious cardiovascular events.
- Exception: known cardiac issues should be referred to cardiology before a stimulant trial.
- Safety of very high dose stimulant is less well established.

Cooper at al. 2011

ADHD and Substance Abuse

- ADHD diagnosis itself increases the risk of substance use and nicotine dependence
- Stimulant misuse rates of 5-9% for grade school and high school (and 5-35% in college-age individuals)
- Consider longer-acting formulations, lisdexamfetamine, and atomoxetine.
- ADHD medications used for adolescents with active substance abuse overall less effective.
Tics and ADHD

- High comorbidity
  - About 60% of tic disorder patients also have ADHD
- Tics are no longer a contraindication for trying stimulants
  - Some experience an exacerbation, if so use alternatives

Cochrane Review, 2011

Treatment Hierarchy

- If stimulants are ineffective, revisit diagnosis
- If feel convinced child has ADHD, move on to other meds
**Atomoxetine**

- Brand name: Strattera
- Noradrenergic reuptake inhibitor
- Once daily or twice daily dosing
- Start at 0.5 mg/kg/day for 2 weeks. Increase as tolerated to ~1.2 mg/kg/day.
  - Maximum 100 mg or 1.4 mg/kg (whichever is less).
- Metabolized by P450 2D6 pathway
  - In other words, fluoxetine and paroxetine can increase blood levels
- Approved ≥6 year old

---

**Atomoxetine**

- Can take up to 6 weeks for benefit
  - Counsel family on delayed effect compared to stimulants.
- Effect size ~0.6 (similar to guanfacine)
  - For comparison, effect size of stimulants approximately 0.9
  - For reference, effect size 0.2 is mild, 0.6 is moderate, and 0.8 is high.
- Consider if
  - Family opposed to stimulants
  - Substance abuse history
  - Late evening behavior problems
  - Stimulants don’t work
Bimodal Atomoxetine Response

![Graph showing change in ADHD total score over weeks for moderate/non-responders (N=318) and much improved responders (N=279).]

Atomoxetine side effects

- GI distress, sedation (insomnia in adults)
- Possible suppression in growth velocity
- Not recommended if cardiac abnormalities
  - Like the stimulants, can increase pulse and blood pressure
- Warning for liver disease (2 reports; none in 6000 patients in clinical trial)
  - Routine monitoring of LFTs not recommended.
- Boxed warning for suicidal thinking (risk of 4/1000 in a large controlled study); no completed suicides
Alpha2 Agonists (clonidine, guanfacine)

- May find more effective for hyperactivity than for inattention
- Sedation, dizziness, hypotension, bradycardia
- Clonidine is more soporific
  - Soporific effect may wane after 2-3 weeks
  - Somewhat reduced clearance when given with an amphetamine
- May not see full benefit for 4-6 weeks
- Review personal and family cardiac history
  - Any risk from causing bradycardia?
- Review risk of rebound hypertension if sudden discontinuation
  - Uncommon risk for kids, but more common risk with adults

Guanfacine

<table>
<thead>
<tr>
<th></th>
<th>Starting dose</th>
<th>Maximum dose</th>
<th>Half Life</th>
<th>FDA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Guanfacine</td>
<td>&lt;45 kg, 0.5 mg qhs;</td>
<td>2 mg (27-40 kg); 3 mg (40-45 kg); 4</td>
<td>14 h</td>
<td>Not approved for</td>
</tr>
<tr>
<td></td>
<td>&gt;45 kg, 1 mg qhs</td>
<td>mg (&gt;45 kg)</td>
<td></td>
<td>ADHD</td>
</tr>
<tr>
<td>Guanfacine extended release (Intuniv)</td>
<td>1 mg daily</td>
<td>7 mg</td>
<td>16 h</td>
<td>Approved 6-17yo</td>
</tr>
</tbody>
</table>

Wait at least one week between dose increases
**Clonidine**

<table>
<thead>
<tr>
<th></th>
<th>Starting dose</th>
<th>Maximum dose</th>
<th>Half life</th>
<th>FDA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clonidine</td>
<td>&lt;45 kg, 0.05 mg qhs</td>
<td>0.2 mg (27-40 kg); 0.3 mg (40-45 kg); 0.4 mg (&gt;45 kg).</td>
<td>12 h</td>
<td>Not approved</td>
</tr>
<tr>
<td>Clonidine extended release (Kapvay)</td>
<td>&gt;45 kg, 0.1 mg qhs</td>
<td>0.4 mg 12-16 h</td>
<td>Approved 6-17yo</td>
<td></td>
</tr>
</tbody>
</table>

Wait at least one week between dose increases.

---

**Guanfacine XR Dose Response Example**

321 6-17 year olds, started at 1mg, increased over 3 weeks to final randomized dose (visit 3), then continued on that dose.

Sallee F et al, 2009
Clonidine XR Example of Reduced Peak

When I Consider $\alpha_2$-Agonists for ADHD

- Stimulants don’t work/not tolerated
- Want to generate a nighttime sedative effect
  - Note bedtime administration of XR forms roughly as effective next day on ADHD symptoms as AM doses
- Want to treat co-morbid tics
- Cardiac concerns or substance abuse that contraindicate stimulants
- Add on to stimulants that aren’t working well enough on their own
  - An FDA approved combination
Other Treatments?

- Bupropion (Wellbutrin)
  - Not FDA approved for pediatric use
  - Combined dopaminergic/noradrenergic mechanism of action
  - Some evidence of ADHD benefits
  - Consider if other primary treatments have failed

- Neurofeedback
  - Early empirical support
    - Mostly used unblinded observer reports of change
    - Subsequent blinded or controlled trial results have not supported the value of neurofeedback

Hobr Mar et al 2014

Essential Fatty Acid Supplements

- Fish Oil
  - Initial studies showed mild range benefits
  - 2012 Cochrane meta-analysis found no clear benefits
  - If trialed, consider 1-2 grams daily with substantial EPA component (eicosapentaenoic acid)

- Diet restrictions
  - Generally does not impact ADHD symptoms
  - Small subset of children may respond to dietary restrictions (elimination diet)
    - Blinded responses are much smaller than unblinded responses
    - Effect sizes were small in these subgroups, such as 0.07 to 0.29

Further supplements

• Melatonin
  • Some evidence of benefit for chronic insomnia with comorbid ADHD
    • Not benefiting core ADHD symptoms
• Iron and Zinc supplementation
  • May have ADHD benefits when child has high risk of dietary deficiency
• Other supplements like Gingko biloba, St John’s Wort, magnesium, and pycnogenol (pine bark) are not well supported treatment options

Bloch and Mulqueen 2014

Physical Exercise

• Review of 16 studies indicates exercise may improve executive functioning and behavioral symptoms associated with ADHD
  • May enhance neural growth and alter gene expression
  • Effect size varied from small to large. Further investigation needed. Concluding causality problematic
  • Appropriate to recommend physical exercise

Questions?

• Call PAL at 866-499-7257 for any future questions!