ADHD Overview and Update

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Disclosures

• Financial: No relevant financial relationships exist.
• Unlabeled/unapproved uses: Off-label medication use is discussed in this presentation, and it will be highlighted when it occurs.
ADHD—adaptive trait (but maybe not for school)

- One ADHD gene (dopamine receptor D4) allele may have conveyed advantage evolutionarily
  - Higher rates found in migratory populations. Maybe this gene encouraged greater innovation/less fearfulness about the challenges of new environments.


Controversy and Innovation...

• Different thinking styles may help with solving the large problems we face today.
  • --risk-taking and innovation when harnessed correctly could offer valuable advantages.

Tasks of the healthcare provider...
• How do we help these children function as their brain controls mature?
• How do we help these adults avoid the dangerous pitfalls of poorly controlled ADHD?
Diagnosis

- Before 12 yo
- 6 months duration
- 2 or more settings
- Clinically significant impairment
- Not explained by other disorder
- 6 symptoms of inattention or hyperactivity or both
  - DSM-5 updates: 5 symptoms for adults, examples included to facilitate diagnoses across the life span, cross-situational requirement strengthened to include several symptoms in each setting, subtypes replaced with specifiers (which map to previous subtypes).

Inattention

- 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

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

Etiology

- Executive function deficit
- Dopaminergic and noradrenergic dysregulation abnormalities
  - Frontal-basal ganglia networks (inferior frontal cortex), supplementary motor area, anterior cingulate cortex, and dorsolateral prefrontal cortex, parietal, and cerebellar areas
    - Heritability 76%
    - Causal relationship with low birth weight (even in full term infants)
    - Substance exposure in utero
    - Brain injury
    - Early deprivation
    - Preterm birth
    - Organophosphate pesticides

Prevalence and Prognosis

- Prevalence 6-9% (2x boys)
  - Female gender protective effect (relevant to family history)
- Many will have symptoms persisting into adulthood.
  - As many as 90% will still have some symptoms of ADHD, not necessarily meeting strict diagnostic criteria.
- Long-term consequences of ADHD:
  - Higher rates of traffic and other accidents, marital difficulties, unemployment, antisocial and criminal behavior, and obesity
  - Lower household income attained
  - Higher rates of attempted and completed suicide (suicide attempters more likely to have ADHD diagnosis than depression)

Comorbidities

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

In general, no testing or imaging is indicated.

Clinical diagnosis
  • But some soft physical signs may be present, such as motor overflow and clumsiness.

Rating scales can help elicit symptoms.

Comparison to peers
  • Inattention/hyperactivity common in preschoolers.

Response to stimulants is not unique to individuals with ADHD.

Consider psychological or neuropsychological testing if low cognitive ability or achievement relative to ability.

Differential Diagnosis

- Other disruptive behavior disorders
- Anxiety disorders
- Affective disorders
- Adjustment disorders
- Developmental speech and language disorders
- Reactive attachment disorder
- Substance abuse
- Trauma
Differential Diagnosis

- If other symptoms present, consider
  - Thyroid
  - Seizures
  - Sleep Disorder
  - Anemia
  - Sensory impairment
  - Brain injury
  - Genetic syndrome
  - Lead

- Medication side effects may mimic ADHD.
  - benzodiazepine, corticosteroids, antihistamines, antipsychotics
Multimodal Treatment of Attention-Deficit/Hyperactivity Disorder 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.

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

- About 1 mg/kg optimal
- Those in combination treatment ended up on lower doses of medication than medication treatment alone group.
  - Medication management 32.3 mg/day
  - Combined care 28.7 mg/day

• After initial 14 months of treatment, patients returned to community care.
• No outcome differences between original treatment groups at 8 years
• Despite *overall maintenance of improvement* in functioning relative to pretreatment, the MTA group as a whole was functioning significantly less well than the non-ADHD classmate sample. Sustained improvement is achievable, but not normalization.
• Children with behavioral, socio-economic, or intellect advantage or best response to treatment have the best prognosis.

Fig. 2 Selected outcome variables for MTA children, graphed by originally randomized treatment group assignment and LNCG. Beh = behavior therapy; CC = community care; CIS = Columbia Impairment Rating Scale; Comb = combined; LNCG = local normative comparison group; MedMgt = medication management; ODD = oppositional defiant disorder; SNAP = Swanson, Nolan, Pelham Rating Scale.

Preschool ADHD Treatment Study (PATS)

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

• 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 at 6 yrs

- 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 steeper symptom decline (but girls’ baseline symptoms more severe).
  - Hint of positive long-term benefit on parent ratings for those who completed the study.

Treatment Recommendations

• Psychoeducation

• Behavioral interventions
  • Rewarding desirable behaviors, non-punitive consequences for negative behaviors

• Parent management training
  • Maintain schedule, organize home, set small goals, limit choices, use charts/lists to maintain focus, encourage successful activities, reduce distractions, use calm discipline
  • Incredible Years Parenting Program, New Forest Parenting Program, Parent-Child Interaction Therapy, Positive Parenting Program
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, occupational therapy tools.
  • Classroom interventions effective in improving achievement scores, but benefits sustained only as long as interventions continued

• Training in skills deficits
  • Organization and planning
  • CBT for adolescents (builds organizational and management skill, set up for success to avoid distractibility, adaptive thinking strategies)

Stimulants

• Medications for ADHD are dopaminergic or noradrenergic.
• Evidence exists for the protective effect of stimulants on comorbid disorders.
  • Depressive and anxiety disorders
  • Disruptive behavior
  • Family quality of life
  • Repeating a grade

Stimulants

• Can start with either a methylphenidate or an amphetamine product
  • Amphetamines FDA approved > or = 3 yo
  • Methylphenidates FDA approved > or = 6 yo
• Similar efficacy
• Side effects may be more pronounced with amphetamine products.
• Push a stimulant dose before moving on to next trial.
  • Avoid unsafe doses.

<table>
<thead>
<tr>
<th>Name</th>
<th>Duration of Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methylphenidate (Ritalin, Methylin)</td>
<td>4-6 h</td>
</tr>
<tr>
<td>D-methylphenidate (Focalin) *2x potency of methylphenidate</td>
<td>4-6 h</td>
</tr>
<tr>
<td>Mixed amphetamine salts (Adderall, Evekeo)</td>
<td>4-6 h</td>
</tr>
<tr>
<td>D-amphetamine (Zenzedi, ProCentra)</td>
<td>4-6 h</td>
</tr>
</tbody>
</table>
## Long Acting Stimulants

<table>
<thead>
<tr>
<th>Name</th>
<th>Mode of Delivery</th>
<th>Duration of Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ritalin SR</td>
<td>Gradual release</td>
<td>4-8 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>Quillivant XR</td>
<td>20% IR, 80% gradual release</td>
<td>8-10h</td>
</tr>
<tr>
<td>Focalin XR</td>
<td>50% IR, 50% 4 h later</td>
<td>Up to 12 h</td>
</tr>
<tr>
<td>Concerta</td>
<td>22% IR, pump</td>
<td>Up to 12 h</td>
</tr>
<tr>
<td>Daytrana patch</td>
<td>Gradual release</td>
<td>3-5 h after removal</td>
</tr>
<tr>
<td>Adderall XR</td>
<td>50% IR, 50% 4 h later</td>
<td>8-12 h</td>
</tr>
<tr>
<td>Dexedrine spansule</td>
<td>50% IR, 50% gradual</td>
<td>10 h</td>
</tr>
<tr>
<td>Vyvanse</td>
<td>Activated in GI tract</td>
<td>10 h</td>
</tr>
</tbody>
</table>

Side Effects

- Appetite decrease, insomnia, headaches, stomachache, dry mouth, emotional lability/aggression, priapism
- Can cause a slowing in growth velocity for weight and height
- Adrenergic effect on heart rate (5bpm in MTA)
- Obtain baseline levels.
- Options: decrease dose, switch, augment (for example, add clonidine or melatonin for sleep)

Cardiac Concerns

• AHA says obtaining ECG reasonable.
• AAP does not recommend routine ECG.
  • Consider ECG when on high dose, combining medications, BP/pulse change from a medication, or any cardiac symptoms.

• ADHD medications do not appear to increase the risk of serious cardiovascular events.
  • 1,200,438 patients with ADHD prescription matched with 2 nonusers; 2,579,104 person years: hazard ratio 0.7.

Cooper at al. ADHD Drugs and Serious Cardiovascular Events in Children and Young Adults. NEJM 2011; 365 (20): 1896-904.
Cardiac Concerns

- Physical exam before initiating stimulant treatment
- Ask about palpitations, syncope, chest pain, exercise intolerance, family history of sudden death under age 35 (including drowning and motor vehicle accidents).
- Patients with known cardiac issues should be referred to cardiology before a stimulant trial.
- During treatment, monitor blood pressure and heart rate and ask about development of cardiac symptoms.

ADHD and Substance Abuse

- ADHD diagnosis increases the risk of substance use and nicotine dependence.
- Early stimulant treatment may reduce or delay the onset of substance use disorder.
  - Recent follow up data from the MTA revealed no harm or benefit from medication treatment in regard to rates of adolescent substance abuse.

ADHD and Substance Abuse

- 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 are not as effective.

Tics and ADHD

• High comorbidity
  • Multi-site international database of 3500 tic disorder patients: 60% also have ADHD

• Stimulants and Tics
  • “Although stimulants have not been shown to worsen tics in most people with tic disorders, they may nonetheless exacerbate tics in individual cases. In these instances, treatment with alpha agonists or atomoxetine may be an alternative.”

  --Cochrane Review, 2011

ADHD and Irritability

- Recent publication from the MTA examined irritability (not headstrong oppositional behavior) and treatment outcomes.
  - Irritability contributed to impairment and showed longitudinal continuity.

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Effect Size</th>
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</thead>
<tbody>
<tr>
<td>Combined treatment</td>
<td>0.82</td>
</tr>
<tr>
<td>Medication management</td>
<td>0.63</td>
</tr>
<tr>
<td>Community comparison</td>
<td>0.48</td>
</tr>
<tr>
<td>Behavioral treatment</td>
<td>0.42</td>
</tr>
</tbody>
</table>

Treatment Hierarchy

- If stimulants are ineffective, revisit diagnosis.
- Use a single medication when possible.
Atomoxetine

- Brand name: Strattera
- Noradrenergic reuptake inhibitor
- Once daily or twice daily dosing
- Start at 0.5 mg/kg/day for 2 weeks. Increase to 1.2 mg/kg/day.
- Maximum 100 mg or 1.4 mg/kg (whichever is less).
- Metabolized by P450 2D6 pathway
- Approved > or = 6 yo

Atomoxetine

• Can be helpful to anxiety

• 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.

**Fig. 1** Temporal course of changes in the Attention-Deficit/Hyperactivity Disorder Rating Scale–IV–Parent Version: Investigator Administered and Scored (ADHD-RS total score). Unlike moderate/nonresponders (filled diamonds), much improved responders (filled squares) experienced sharp decreases (i.e., improvements) in the ADHD-RS total score within the first 1 to 4 weeks, with continued divergence at later time points. *p < .001 at each time point across response groups by week.
Atomoxetine side effects

- GI distress, sedation (insomnia in adults)
- Possible suppression in growth velocity
- Not recommended if structural cardiac abnormalities, cardiomyopathy, or rhythm abnormalities
- Warning for liver disease (2 reports; none in 6000 patients in clinical trial)
  - Monitoring of LFTs not recommended.
- Boxed warning for suicidal thinking (risk of 4/1000 in a large controlled study); no completed suicides

Alpha agonists

• May be more effective for hyperactivity than inattention
• Clonidine more soporific; guanfacine may be better for inattention
• Soporific effect may wane after 2-3 weeks
• May not see full benefit for 4-6 weeks
• Sedation, dizziness, hypotension, bradycardia
• Review personal and family cardiac history
• Review risk of rebound hypertension
## 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;45kg, 0.5 mg qhs; &gt;45 kg, 1 mg qhs</td>
<td>2 mg (27-40 kg); 3 mg (40-45 kg); 4 mg (&gt;45 kg)</td>
<td>14 h</td>
<td>Not approved</td>
</tr>
<tr>
<td>Guanfacine extended</td>
<td>1 mg daily</td>
<td>4 mg (7 mg for 13-17 year olds)</td>
<td>16 h</td>
<td>Approved 6-17yo</td>
</tr>
<tr>
<td>release (Intuniv)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Wait 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;45kg, 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</td>
<td>12-16 h</td>
<td>Approved 6-17yo</td>
</tr>
</tbody>
</table>

Wait one week between dose increases.

Clonidine

Clonidine

- Sudden death in four youths receiving clonidine and methylphenidate.
  - No causality established. No other cases identified.
  - Reduce MPH dose by 40% when combined with clonidine. Consider ECG.
- High profile case of death of 4 yo girl in Massachusetts on clonidine. Parents administered doses above prescribed; convicted of murder.
  - Advise families about importance of following dosing instructions exactly.
  - Consider care-giving environment of child.
  - Monitor frequency of refills.

Bupropion

- Brand name: Wellbutrin
- Not FDA approved for pediatric use
- Combined dopaminergic/noradrenergic mechanism of action
- Consider when primary treatments have failed or in patients with co-occurring mood disorders, substance abuse, or smoking.
Bupropion

- Side effects: insomnia, appetite decrease, less commonly tics, seizures
- Risk of drug induced seizures increases 10x at doses > 450 mg/day
- Starting dose less than 150 mg/day or 3mg/kg/day
- Maximum dose less than 300 mg/day or 6 mg/kg/day
- No single dose greater than 150 mg

Omega 3

- Not FDA approved.
- Meta-analysis of 699 patients—small but significant effect (effect size 0.31)
- Additional recent meta-analyses also support benefit
- Can be used to augment traditional pharmacologic interventions or for families that decline other pharmacologic options
- Look for EPA doses between 450 mg and 600 mg

Vitamin D

• Possible improvement from Vitamin D supplementation. Small study.

Impact of Vitamin D Supplementation on ADHD in Children; Annals of Pharmacotherapy; Elshorbagy et al; 2018.
Dietary intervention

• Recent meta-analysis showed some mild benefit from elimination of food color from diet.
  • But effects may be limited to those with suspected food sensitivities.
• Elimination diet did not demonstrate significant benefit.

Neurofeedback

- Frequency band training—association of increased theta activity (4-8 Hz) and reduced beta activity (>13 Hz) compared to non-affected peers
- Slow cortical potential training—targets cortical excitation thresholds
- Neurofeedback computer program provides immediate feedback based on EEG activity, and children learn to induce the desired brain activity.
- Review of 15 studies (only 4 randomized) including 1100 children shows benefits to impulsivity and inattention.
- Recent high quality meta-analysis fails to support neurofeedback as an effective treatment for ADHD.

Computer training

• Small studies thus far
• Some indication of improvement, often targeting existing specific neuropsychological deficits (working memory)
• Improvement on student self-rating, parent and teacher ratings not consistent
• School-based interventions promising concept
• Need additional larger studies

Physical Exercise

- Recent review (16 studies combined) 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.

Management Wrap up

- Make only 1 change at a time to correctly attribute benefit and side effects.
- Assess after 1 year whether on-going treatment is needed.
Questions? Call PAL.

877-501-7257

www.seattlechildrens.org/PAL