ADHD Overview and Update

PAL Program Educational Event
April 9th, 2016
Jackson, WY

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Disclosures

• Unlabeled/unapproved uses: Off-label medication use is discussed in this presentation, and it will be highlighted when it occurs.
## Disclosure of Potential Conflicts

<table>
<thead>
<tr>
<th>Source</th>
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<td>Research Funding</td>
<td>Pfizer, Shire, Ironshore Pharmaceuticals</td>
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<td>Advisor/ Consultant</td>
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OBJECTIVES

• Be able to describe current best practices and empirically-supported new treatments for ADHD.
• Be able to identify side effects for common ADHD medications.
• Be able to identify ways to coordinate care and monitor treatment response in order to optimize outcomes.
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 (even today)! Maybe this gene encouraged greater innovation/less fearfulness about the challenges of new environments.

Source of controversy...

- NY Times search of “ADHD”:
  - Difficult Decisions in Treating ADHD (November 2014)
  - A Natural Fix for ADHD (October 2014)
  - Thousands of Toddlers are Medicated for ADHD (May 2014)
  - Reports Says Medications Use is Rising for Adults with ADHD (May 2014)
  - How We Diagnose and Treat ADHD (March 2014)
  - Expand Pre-K, Not ADHD (February 2014)
  - Doctors Train to Spot Signs of ADHD (February 2014)
  - Untangling the Myths About Attention Disorder (March 2016)

Other media:
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?
Is Adult ADHD a Childhood-Onset Neurodevelopmental Disorder? Evidence From a Four-Decade Longitudinal Cohort Study

Terrie E. Moffitt, Ph.D., Renate Houts, Ph.D., Philip Asherson, M.D., Daniel W. Belsky, Ph.D., David L. Corcoran, Ph.D., Maggie Hammerle, B.A., Honalee Harrington, B.A., Sean Hogan, M.S.W., Madeline H. Meier, Ph.D., Guilherme V. Polanczyk, M.D., Richie Poulton, Ph.D., Sandhya Ramrakha, Ph.D., Karen Sugden, Ph.D., Benjamin Williams, B.A., Luis Augusto Rohde, M.D., Avshalom Caspi, Ph.D.

Objective: Despite a prevailing assumption that adult ADHD is a childhood-onset neurodevelopmental disorder, no prospective longitudinal study has described the childhoods of the adult ADHD population. The authors report follow-back analyses of ADHD cases diagnosed in adulthood, alongside follow-forward analyses of ADHD cases diagnosed in childhood, in one cohort.

Method: Participants belonged to a representative birth cohort of 1,037 individuals born in Dunedin, New Zealand, in 1972 and 1973 and followed to age 38, with 95% retention. Symptoms of ADHD, associated clinical features, comorbid disorders, neuropsychological deficits, genome-wide association study-derived polygenic risk, and life impairment indicators were assessed. Data sources were participants, parents, teachers, informants, neuropsychological test results, and administrative records. Adult ADHD diagnoses used DSM-5 criteria, apart from onset age and cross-setting corroboration, which were study outcome measures.

Results: As expected, childhood ADHD had a prevalence of 6% (predominantly male) and was associated with childhood comorbid disorders, neurocognitive deficits, polygenic risk, and residual adult life impairment. Also as expected, adult ADHD had a prevalence of 3% (gender balanced) and was associated with adult substance dependence, adult life impairment, and treatment contact. Unexpectedly, the childhood ADHD and adult ADHD groups comprised virtually nonoverlapping sets; 90% of adult ADHD cases lacked a history of childhood ADHD. Also unexpectedly, the adult ADHD group did not show tested neuropsychological deficits in childhood or adulthood, nor did they show polygenic risk for childhood ADHD.

Conclusions: The findings raise the possibility that adults presenting with the ADHD symptom picture may not have a childhood-onset neurodevelopmental disorder. If this finding is replicated, then the disorder’s place in the classification system must be reconsidered, and research must investigate the etiology of adult ADHD.

Diagnosis

- Before 12 years old
- 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

- Blurs 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)
- 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

Fliers et al. ADHD Is a Risk Factor for Overweight and Obesity in Children; J Develop & Behavior Peds 2013; 34:566-574.
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

Work-up

• 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.

Work-up

• If other symptoms present, consider
  • Lead
  • Thyroid
  • Seizures
  • OSA
  • Anemia
  • Trauma
  • Substance abuse
  • Sensory impairment
  • Brain injury
  • Genetic syndrome

• Medication side effects may mimic ADHD.
  • Bronchodilators
  • Corticosteroids
  • Antihistamines
  • Antipsychotics
Multimodal Treatment of Attention-Deficit/Hyperactivity Disorder Study (MTA)

• 600 children, 7-9 years old
• 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

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
- 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.

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 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
• Training in skills deficits
  • 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, 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)
The UW Integrated Care Model

- PCP
- Patient
- BHP/Care Manager
- Consulting Psychiatrist
- Other Behavioral Health Clinicians
- Substance Treatment, Vocational Rehabilitation, CMHC, Other Community Resources

New Roles
Core Program
Additional Clinic Resources
Outside Resources
Behavioral Parent Training *
- oppositionality, aggression,
- negative parenting, family conflict,
- positive parenting, parent self-efficacy

Behavioral Peer Interventions
- prosocial behavior, peer acceptance, on-task time
- peer rejection, aggression

Organization Skills Training *

Preschool (2-5)  School Age (6-12)  Adolescence (13-18)

Behavioral Parent Training *
Behavior Classroom Management *
- academic productivity, peer relations, adaptive behavior
- oppositionality, aggression

Behavioral Peer Interventions *
Organization Skills Training
- organization skills, homework completion, family function, grades

*Figure 1. Functional Outcomes of “Well Established” Psychosocial Treatments for ADHD Throughout Development.
*Treatments to be prioritized for this developmental period
Treatment Sequencing for Childhood ADHD: A Multiple-Randomization Study of Adaptive Medication and Behavioral Interventions

- Behavioral and pharmacological treatments for children with attention deficit/hyperactivity disorder (ADHD) were evaluated to address whether endpoint outcomes are better depending on which treatment is initiated first and, in case of insufficient response to initial treatment, whether increasing dose of initial treatment or adding the other treatment modality is superior.

- Children with ADHD (ages 5-12, N = 146, 76% male) were treated for 1 school year. Initially randomized to parent management training or low dose methylphenidate. After 8 weeks insufficient responders were re-randomized to secondary interventions that either increased the dose/intensity of the initial treatment or added the other treatment.

- The group beginning with behavioral treatment displayed significantly lower rates of observed classroom rule violations (the primary outcome) at study endpoint and tended to have fewer out-of-class disciplinary events. Further, adding medication secondary to initial behavior modification resulted in better outcomes on the primary outcomes and parent/teacher ratings of oppositional behavior than adding behavior modification to initial medication.

- Normalization rates on teacher and parent ratings were generally high. Parents who began treatment with behavioral parent training had substantially better attendance than those assigned to receive training following medication. Beginning treatment with behavioral intervention produced better outcomes overall than beginning treatment with medication.

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.

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<tr>
<th>Name</th>
<th>Duration of Action</th>
<th>Notes</th>
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<tbody>
<tr>
<td>Methylphenidate (Ritalin, Methylin)</td>
<td>4-6 h</td>
<td></td>
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<tr>
<td>D-methylphenidate (Focalin)</td>
<td>4-6 h</td>
<td>*2x potency of methylphenidate</td>
</tr>
<tr>
<td>Mixed amphetamine salts (Adderall)</td>
<td>4-6 h</td>
<td></td>
</tr>
<tr>
<td>D-amphetamine (Zenzedi, ProCentra)</td>
<td>4-6 h</td>
<td>Liquid 5 mg/5 ml Approved ages 3-5</td>
</tr>
<tr>
<td>Methamphetamine Desoxyn</td>
<td>4-6 h</td>
<td>FDA-indicated for ADHD and obesity</td>
</tr>
<tr>
<td>Amphetamine (Evekeo)</td>
<td>4-6 h</td>
<td>Approved ages 3-5 FDA-indicated for ADHD, obesity, and narcolepsy</td>
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## Long Acting Stimulants

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<tr>
<th>Name</th>
<th>Mode of Delivery</th>
<th>Duration of Action</th>
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<td>Ritalin SR, Metadate ER, Methylin ER</td>
<td>Gradual release</td>
<td>4-8 h</td>
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<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 (dextroamphetamine)</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>
<tr>
<td>Aptensio XR (methylphenidate)</td>
<td>40% IR, 60% ER (may be sprinkled)</td>
<td>12 h</td>
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Epocrates, accessed 3.2.2016
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 (eg, 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

NEW RESEARCH

Treatment of Children With Attention-Deficit/Hyperactivity Disorder (ADHD) and Irritability: Results From the Multimodal Treatment Study of Children With ADHD (MTA)

Lorena Fernández de la Cruz, PhD, Emily Simonoff, MD, James J. McGough, MD, Jeffrey M. Halperin, PhD, L. Eugene Arnold, MD, MEd, Argyris Stringaris, MD, PhD, MRCPsych

Objective: Clinically impairing irritability affects 25% to 45% of children with attention-deficit/hyperactivity disorder (ADHD); yet, we know little about what interventions are effective in treating children with ADHD and co-occurring irritability. We used data from the Multimodal Treatment Study of Children With ADHD (MTA) to address 3 aims: to establish whether irritability in children with ADHD can be distinguished from other symptoms of oppositional defiant disorder (ODD); to examine whether ADHD treatment is effective in treating irritability; and to examine how irritability influences ADHD treatment outcomes.

Method: Secondary analyses of data from the MTA included multivariate analyses, and intent-to-treat random-effects regression models were used.

Results: Irritability was separable from other ODD symptoms. For treating irritability, systematic stimulant treatment was superior to behavioral management but not to routine community care; a combination of stimulants and behavioral treatment was superior to community care and to behavioral treatment alone, but not to medication alone. Irritability did not moderate the impact of treatment on parent- and teacher-reported ADHD symptoms in any of the 4 treatment groups.

Conclusion: Treatments targeting ADHD symptoms are helpful for improving irritability in children with ADHD. Moreover, irritability does not appear to influence the response to treatment of ADHD.

Clinical trial registration information—Multimodal Treatment Study of Children With Attention Deficit and Hyperactivity Disorder (MTA); http://www.clinicaltrials.gov; NCT00000388.

Key Words: irritability, attention-deficit/hyperactivity disorder, oppositional defiant disorder, treatment outcomes

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.

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<th>Intervention</th>
<th>Effect Size</th>
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<tr>
<td>Combined treatment</td>
<td>0.82</td>
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<tr>
<td>Medication management</td>
<td>0.63</td>
</tr>
<tr>
<td>Community comparison</td>
<td>0.48</td>
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<tr>
<td>Behavioral treatment</td>
<td>0.42</td>
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Stimulant Medications and Sleep for Youth With ADHD: A Meta-analysis

Katherine M. Kidwell, MA, Tori R. Van Dyk, MA, Alyssa Lundahl, MA, Timothy D. Nelson, PhD

abstract

**CONTEXT:** Mixed findings exist on whether stimulant medications alter youth sleep.

**OBJECTIVE:** To determine the effect of stimulant medications on sleep.

**DATA STUDIES:** Studies published through March 2015 were collected via CINAHL, PsycINFO, and PubMed. References of retrieved articles were reviewed.

**STUDY SELECTION:** Eligibility criteria included studies with children/adolescents who had attention-deficit/hyperactivity disorder (ADHD), random assignment to stimulants, and objective sleep measurement. Studies that did not include information about key variables were excluded.

**DATA EXTRACTION:** Study-level, child-level, and sleep data were extracted by 2 independent coders. Effect sizes were calculated by using random effects models. Potential moderators were examined by using mixed effect models.

**RESULTS:** A total of 9 articles (N = 246) were included. For sleep latency, the adjusted effect size (0.54) was significant, indicating that stimulants produce longer sleep latencies. Frequency of dose per day was a significant moderator. For sleep efficiency, the adjusted effect size (−0.32) was significant. Significant moderators included length of time on medication, number of nights of sleep assessed, polysomnography/actigraphy, and gender. Specifically, the effect of medication was less evident when youth were taking medication longer. For total sleep time, the effect size (−0.59) was significant, such that stimulants led to shorter sleep duration.

**LIMITATIONS:** Limitations include few studies, limited methodologic variability, and lack of unpublished studies.

**CONCLUSIONS:** Stimulant medication led to longer sleep latency, worse sleep efficiency, and shorter sleep duration. Overall, youth had worse sleep on stimulant medications. It is recommended that pediatricians carefully monitor sleep problems and adjust treatment to promote optimal sleep.

Treatment Hierarchy

- If IR is not tolerated or ineffective, try XR and vice versa.
- If first stimulant class is unsuccessful, try the other class.
- If stimulants are ineffective, revisit diagnosis before proceeding to non-stimulants.
- Use a single medication when possible.
- Consider adding alpha agonists if response is suboptimal but increasing stimulant not possible due to side effects.
- Adding Strattera to stimulant generally not advised but may be useful in certain cases.
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

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<tr>
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<th>Starting dose</th>
<th>Maximum dose</th>
<th>Half life</th>
<th>FDA</th>
</tr>
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<tbody>
<tr>
<td>Guanfacine</td>
<td>&lt;45kg, 0.5 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>
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<tr>
<td></td>
<td>&gt;45 kg, 1 mg qhs</td>
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<tr>
<td>Guanfacine</td>
<td>1 mg daily</td>
<td>4 mg</td>
<td>16 h</td>
<td>Approved 6-17yo</td>
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<tr>
<td>extended</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>release (Intuniv)</td>
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Wait one week between dose increases.

# Clonidine

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<tr>
<th></th>
<th>Starting dose</th>
<th>Maximum dose</th>
<th>Half life</th>
<th>FDA</th>
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<tr>
<td>Clonidine</td>
<td>&lt;45 kg, 0.05 mg qhs; &gt;45 kg, 0.1 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</td>
<td>0.1 mg qhs; doses greater than 0.1 mg should be bid</td>
<td>0.4 mg</td>
<td>12-16 h</td>
<td>Approved 6-17yo</td>
</tr>
<tr>
<td>release (Kapvay)</td>
<td></td>
<td></td>
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Wait one week between dose increases.

Clonidine

http://www.kapvay.com/Kapvay_final_09.28.10.pdf
Prescribing information.
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 3 mg/kg/day
- Maximum dose less than 300 mg/day or 6 mg/kg/day
- No single dose greater than 150 mg

<table>
<thead>
<tr>
<th>Treatment strategies for specific side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sedation</strong></td>
</tr>
<tr>
<td>• Give medication at bedtime.</td>
</tr>
<tr>
<td><strong>Orthostatic hypotension/dizziness/high blood pressure</strong></td>
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<tr>
<td>• Adequate hydration</td>
</tr>
<tr>
<td>• Sit-stand-get up slowly</td>
</tr>
<tr>
<td>• Lower dose of medication</td>
</tr>
<tr>
<td>• Consider switching medication, if persists</td>
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<tr>
<td><strong>GI distress/nausea</strong></td>
</tr>
<tr>
<td>• This often improves or resolves over 1-2 weeks</td>
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<tr>
<td>• Take with meals</td>
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<tr>
<td>• Consider antacids or H2 blockers</td>
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<tr>
<td><strong>Activation/jitters/tremors/dystonia</strong></td>
</tr>
<tr>
<td>• Start with small doses or short acting stimulants</td>
</tr>
<tr>
<td>• This may improve or resolve over 1-2 weeks</td>
</tr>
<tr>
<td>• Reduce dose</td>
</tr>
<tr>
<td>• Consider switching medications</td>
</tr>
<tr>
<td>• Consider comorbidities</td>
</tr>
<tr>
<td><strong>Headache</strong></td>
</tr>
<tr>
<td>• Lower dose</td>
</tr>
<tr>
<td>• Try acetaminophen</td>
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<tr>
<td><strong>TICS</strong></td>
</tr>
<tr>
<td>• Reduce dose</td>
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<tr>
<td>• Try another class of stimulants</td>
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<tr>
<td>• Alpha agonist</td>
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<tr>
<td><strong>Insomnia</strong></td>
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<tr>
<td>• Bedtime routine</td>
</tr>
<tr>
<td>• Reduce or eliminate afternoon dose</td>
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<tr>
<td>• Change to early doses in the day</td>
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<tr>
<td>• Reduce dose</td>
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<tr>
<td>• Late night meals</td>
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<tr>
<td>• Restrict caffeine</td>
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<tr>
<td>• Consider low dose alpha agonists – clonidine 0.05mg or guanfacine 0.5mg, dose at bedtime.</td>
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<tr>
<td><strong>Behavioral rebound</strong></td>
</tr>
<tr>
<td>• Try sustained – release stimulant</td>
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<tr>
<td>• Add reduced dose in late afternoon</td>
</tr>
<tr>
<td>• Alpha agonist</td>
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<tr>
<td>Issue</td>
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<tr>
<td>----------------------------------------------------------------------</td>
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<tr>
<td>Weight loss and loss of appetite</td>
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</tr>
<tr>
<td>Psychosis/ depression/ euphoria/mania</td>
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<tr>
<td>Kid off meds over summer</td>
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<tr>
<td>Morning routine difficult until stimulant kicks in</td>
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<tr>
<td>Concerns for stimulant diversion are present</td>
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<tr>
<td>Concerns for substance abuse present</td>
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<tr>
<td>Patient complains of increased anxiety while taking stimulant</td>
</tr>
<tr>
<td>Patient with history of in utero exposure has problems with attention, hyperactivity, and impulsiveness</td>
</tr>
</tbody>
</table>
Omega 3

- Not FDA approved.
- Meta-analysis 699 patients--small but significant effect (effect size 0.31)
- Additional recent meta-analyses also support benefits
- 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

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

- ADHD: increased theta activity (4-8 Hz) and reduced beta activity (>13 Hz) compared to non-affected peers.
- 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.
- Other recent high quality meta-analyses notes additional blinded assessments needed before neurofeedback can be supported as a 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

Qbtech--QbTest is an FDA-cleared device used for assessing the core symptoms of ADHD: hyperactivity, inattention and impulsivity.

1. Objective measures of all three ADHD core symptoms
2. A 15 to 20 minutes test with instant analysis
3. Clear reports with unbiased norm group comparison

QbTest is a test to evaluate the symptoms of ADHD for children and adults that combines motion-tracking analysis with a uniquely designed continuous performance task.

During the 15-20 minute task, the patient is instructed to respond as quickly and accurately as possible to certain geometric shapes appearing on a computer screen by pressing a responder button. As the patient performs the task, a camera located above the computer records movement from a reflector located on the patient's forehead.
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.

At SCH, Fitbit study conducted to assess affect of physical exercise on ADHD symptoms and functioning.

Management Wrap up

• Obtain a baseline of somatic symptoms, sleep, and appetite before beginning medication treatment to avoid attributing baseline characteristics to medication side effects.
• Obtain baseline and post-treatment symptom and functional status from multiple informants using validated measures (eg, Vanderbilt, Conner’s)
• Use a single medication when possible. Make only 1 change at a time to correctly attribute benefit and side effects.
• Assess after 1 year whether on-going treatment is needed.
• Medication holidays may be helpful for weight recovery and to assess need for ongoing treatment; exercise caution when restarting medication at its previous dose.
• Treatment into adult years may be necessary based upon functional needs and ongoing impairment.