Update on Treating ADHD

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To review

- Current understandings about the neurobiology of ADHD
- Mechanisms of action of commonly prescribed ADHD medications
- Practical tips for prescribing and monitoring medications
- New medication options currently under investigation
Neurobiology of ADHD

ADHD

Basic Processes

Executive Function
- Working memory
- Behavioral inhibition

Motivation
- Delay aversion
- Reinforcement

Neural Mechanisms

PFC

Basal ganglia

Cerebellum

Noradrenalin

Dopamine

Serotonin

Genes

<table>
<thead>
<tr>
<th>Gene</th>
<th>DBH</th>
<th>HTR1B</th>
<th>DAT1</th>
<th>D4</th>
<th>D5</th>
<th>SER T</th>
<th>SNAP-25</th>
</tr>
</thead>
</table>

PFC = prefrontal cortex.
Behavioral disinhibition, emotional ability and emergence of diagnosis in preschool years

Prodrome: hyperactivity; and speech, language and motor coordination problems

Full expression of ADHD, psychiatric comorbidity, school failure, peer rejection and neurocognitive dysfunction

Inattention persists and hyperactive–impulsive symptoms wane

Substance abuse, low self-esteem and social disability

Different genetic risk factors affect the course of ADHD at different stages of the lifespan

Psychosocial influences, chaotic family environments, peer influences and mismatch with school and/or work environments

In utero

Genetic predisposition

Fetal exposures and epigenetic changes

Psychosocial influences, chaotic family environments, peer influences and mismatch with school and/or work environments

Different genetic risk factors affect the course of ADHD at different stages of the lifespan

Frontal–subcortical–cerebellar dysfunction via structural and functional brain abnormalities and downregulation of catecholamine systems that regulate attention, reward, executive control and motor functions

Persistence of cortical thickness, default-mode network and white matter tract abnormalities

Schematic representation of functional circuits involved in the pathophysiology of ADHD
Regulation of Attention and Emotion

Regulation of Attention and Emotion
The Prefrontal Cortex Requires a Proper Level of Catecholamines for Optimal Function

Guided attention and responses
Focused, organized and flexible
(eg, Optimally treated ADHD)

NE $\alpha_{2A}$
Moderate $D_1$

Too little $\alpha_{2A}/D_1$

NE $\alpha_1$, $\beta_1$
Excess $D_1$

Misguided attention / responses
Mental inflexibility, stimulus bound
(eg, Excessive dose of stimulant)

Unguided attention / responses
Distracted, poor impulse control
(eg, Untreated ADHD)

Increasing Levels of Catecholamine Release

Drowsy Alert Stressed

Treatment Modalities for ADHD

- Medical Interventions
- Educational / Workplace Interventions
- Psychosocial Interventions

Pharmacologic Treatments for ADHD

**Primary Agents**
- Stimulants
- Atomoxetine
- $\alpha$ adrenergic agonists

**Secondary Agents**
- Bupropion
- Modafanil
- Tricyclic antidepressants

**Adjunctive agents**
- Mood stabilizers
- Anxiolytics
- SSRIs
- Neuroleptics
- Combination regimens
## Child and Adolescent ADHD: Effect Sizes*

<table>
<thead>
<tr>
<th>Medication</th>
<th>Effect Size</th>
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<tbody>
<tr>
<td>Amphetamine</td>
<td>0.92</td>
</tr>
<tr>
<td>Methylphenidate</td>
<td>0.80</td>
</tr>
<tr>
<td>Atomoxetine</td>
<td>0.73</td>
</tr>
<tr>
<td>Modafinil</td>
<td>0.49</td>
</tr>
<tr>
<td>Bupropion</td>
<td>0.32</td>
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</table>

29 controlled studies; N = 4465 children and adolescents

*Drugs used to treat ADHD were evaluated for efficacy using 17 outcome measures. Effect sizes for stimulants (amphetamine and methylphenidate) are significantly greater than are those for other medications.

Adult ADHD: Effect Sizes (Stimulants)

Meta-analyses of 18 randomized controlled trials
5 RCT of ER stimulants in adults (2006 - 2008)
  • Mean effect size (ES) = 0.73
  • N=1 d-MPH ER; LDX; MAS XR; N=2 OROS MPH
  • No heterogeneity of effect size

“documents the robust efficacy of stimulant medications in adult ADHD similar to observed in children”

Faraone J Clin Psychiatry 2010
Neurotransmitters & ADHD Medications

dopamine

norepinephrine

atomoxetine

amphetamine

methylphenidate

atomoxetine
### Pharmacologic Treatments Approved for ADHD

<table>
<thead>
<tr>
<th>Amphetamine-based Formulations</th>
<th>Duration of Effect</th>
<th>Peds/Adult</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adderall® (mixed amphetamine salts)</td>
<td>4-6 hours</td>
<td>+/-</td>
</tr>
<tr>
<td>Adderall XR® (mixed amphetamine salts XR)</td>
<td>~12 hours</td>
<td>+/-/++</td>
</tr>
<tr>
<td>Dexedrine® Spansule (dextroamphetamine)</td>
<td>6-8 hours</td>
<td>+/-</td>
</tr>
<tr>
<td>Vyvanse™ (lisdexamfetamine)</td>
<td>~12 hours</td>
<td>+/-/+</td>
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<table>
<thead>
<tr>
<th>Methylphenidate-based Formulations</th>
<th>Duration of Effect</th>
<th>Peds/Adult</th>
</tr>
</thead>
<tbody>
<tr>
<td>Concerta® (MPH)</td>
<td>~12 hours</td>
<td>+/-/++</td>
</tr>
<tr>
<td>Daytrana® (MPH patch)</td>
<td>~12 hours (worn for 9)</td>
<td>+/-</td>
</tr>
<tr>
<td>Focalin® (dexMPH capsule)</td>
<td>~5 hours</td>
<td>+/-</td>
</tr>
<tr>
<td>Focalin® XR (dexMPH XR capsule)</td>
<td>10-12 hours</td>
<td>+/-</td>
</tr>
<tr>
<td>Metadate® CD (MPH controlled-release capsule)</td>
<td>8-10 hours</td>
<td>+/-</td>
</tr>
<tr>
<td>Ritalin® (MPH)</td>
<td>~4 hours</td>
<td>+/-</td>
</tr>
<tr>
<td>Ritalin® LA (MPH XR capsule)</td>
<td>8-10 hours</td>
<td>+/-</td>
</tr>
<tr>
<td>Quillivant XR™ (MPH XR liquid)</td>
<td>~12 hours</td>
<td>+/-</td>
</tr>
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<table>
<thead>
<tr>
<th>Nonstimulants</th>
<th></th>
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<tbody>
<tr>
<td>Strattera® (atomoxetine)</td>
<td>8-24 hours</td>
<td>+/-/+</td>
</tr>
<tr>
<td>Intuniv® (guanfacine XR)</td>
<td>~12 hours</td>
<td>+/-</td>
</tr>
<tr>
<td>Kapvay® (clonidine XR)</td>
<td>~12 hours</td>
<td>+/-</td>
</tr>
</tbody>
</table>

Recent FDA Approved Medications

- **Evekeo®** (AMP racemic)
- **Aptensio XR®** (MPH)
- **Oral Disintegrating**
  - Adzenys XR-ODT® (MPH)
- **Liquids**
  - ProCentra® (AMP)
  - Dyanavel XR® (AMP)
  - Methylin® (MPH)
- **Chewable**
  - QuillChew® ER (MPH)

AMPH = amphetamine; MPH = methylphenidate.
US Food and Drug Administration.
Pharmacologic Treatments for ADHD

**Primary Agents**
- **Stimulants**
- Atomoxetine
- \(\alpha\) adrenergic agonists

**Secondary Agents**
- Bupropion
- Modafanil
- Tricyclic antidepressants

**Adjunctive agents**
- Mood stabilizers
- Anxiolytics
- SSRIs
- Neuroleptics
- Combination regimens
Psychostimulants: Overview

- Psychostimulants first-line agents
  - *Multiple FDA approved agents (adult)*
- Long-acting preparations preferable
  - Better adherence, treat through the day
  - Minimize potential for misuse or abuse
- May be useful to orient according to weight
  - eg, 1–1.5 mg/kg/day MPH ~ 70–100 mg/day;
  - 0.5–1.0 mg/kg/day MAS

MAS = mixed amphetamine salts.
Psychostimulants: Overview

- Adverse effects are generally well tolerated
  - Reduced appetite and consequent weight loss
  - Abdominal pain, nausea, constipation
  - Difficulty falling asleep
  - Mild increase in heart rate and blood pressure
  - Jitteriness, jumpiness
  - Motor tics
  - Dysphoria, moodiness, irritability
  - Rebound effects

Summary of Stimulant Action

Methylphenidate
- Blocks reuptake of transmitter into pre-synaptic terminal

Amphetamine
- Releases transmitter from vesicle
- Blocks reuptake of transmitter into vesicle
- Blocks reuptake of transmitter into pre-synaptic terminal
- Induces release of transmitter when it is absorbed into the pre-synaptic terminal
- D- form acts on DA neurons; L-form acts on NE neurons
Methylphenidate Activates Dorsal Anterior Mid-cingulate Cortex

- fMRI at baseline and again at week 6
- OROS MPH group showed higher daMCC activation at 6 weeks vs placebo
- N=21 adults with ADHD; dosing to 1.3 mg/kg/day OROS MPH or placebo

Psychostimulant Use Guidelines

- Trust your patient – if you are concerned about potential substance abuse or misuse do not prescribe stimulants
- Explain the principle of a “medication trial” and the need for patient to keep a medication response log
- Up to 30% of patients respond better to either AMPH or MPH, while 30% respond equally well to both
- Start with MPH at varying doses – once the optimal dose is determined, can adjust the schedule with longer acting preparations
- If MPH is not optimally effective, switch to AMPH and determine responses to variable doses

Most patients (n=152/174; 87%) responded to either methylphenidate and/or amphetamine\(^1\)


Adjusting Medication

• Some patients report a need for additional medication at specific times
  – Stimulant dose may be increased when there is a need for increased focus
  – Patients who need evening treatment may benefit from
    • Combination of extended-release and immediate-release stimulant
    • Atomoxetine or a combination of atomoxetine and a daytime stimulant

Medication Dosing Options

Stimulants may be prescribed in combination with a nonstimulant to ensure coverage into the evening.

Adapted from Hazell P. CNS Drugs. 2007;21(1):37-46.
Managing Common Side Effects: Appetite Loss

- Patience
  - Usually improves after a few days
- Eat a big breakfast and dinner
  - Absorption?
- Adjust timing of medication
- Adjust timing of meals
- Encourage snacks (including bedtime)
- Consider changing dose, regimen, or medication

Managing Common Side Effects: Insomnia

- For stimulant-induced insomnia
  - Melatonin
  - Clonidine, guanfacine
  - Trazodone
  - Mirtazapine
  - Antihistamine (acutely)
  - Tricyclic antidepressant

The use of these medications for this indication is off-label.

Managing Common Side Effects: Stomachaches

- Direct vs indirect effect
  - Medication vs hunger
  - Determine time of day

- Patience
  - Often resolve after the first few days of treatment

- Lower daily dose

- Try a different medication
Managing Common Side Effects: Tics

- Stimulant-exacerbated tics
  - Examine severity of tics
  - Re-challenge to examine if tics are stimulant-induced
  - Switch to atomoxetine, $\alpha_2$-adrenergic agonists, or atypical or typical antipsychotics (pimozide – FDA approved)
  - Combination therapies
    - Atomoxetine plus stimulant
    - Clonidine plus methylphenidate (3 studies)
    - Atypical plus other treatment

The use of these medications for this indication is off-label.

Recent Concerns about Stimulants and Cardiac Disease

- Current FDA language stipulates that sudden death can occur at usual doses in patients with a pre-existing structural cardiac abnormality or other serious heart problem.
- Careful history of heart-related problems must be obtained and documented before starting stimulant medication.
Important screening questions:

• Patient-related factors: history of murmur, syncope, or other CVD illness
• Family-related factors: history of early or sudden cardiac death
• Other health considerations that increase CVD risk
  – Smoking history, caffeine use, over-the-counter sympathomimetic medications
• If cardiac screening is negative, EKG is NOT required prior to initiating treatment

CVD = cardiovascular disease; EKG = electrocardiogram.
Clinical Assessment of Cardiac Risk

- Spontaneous syncope
- Exercise-induced syncope
- Exercise-induced chest pain
- Sudden death in family member under age 30
- History of cardiac abnormalities (structural or electrical) in self or family members
- EKGs are not routinely required

Treating ADHD Patients with Heart Disease

- Possible causes for concern
  - History of palpitations or arrhythmia
  - Recent myocardial infarction
  - Syncopal episodes, dizziness
  - Multiple risk factors, such as smoking, high body mass index, hypertension, metabolic syndrome
- Maximize cardiac medications and address risk factors; patients with ADHD may find it difficult to make necessary lifestyle changes
- Introduce ADHD medication at a low dose and titrate up slowly
- Monitor symptoms, blood pressure/heart rate regularly
- Longer term effects of ADHD medications on cardiovascular status unclear

Treating ADHD Patients with Hypertension

- Evaluate blood pressure/pulse prior to initiating ADHD treatment
- Address hypertension before treating ADHD
- Once hypertension is controlled, treat ADHD and monitor blood pressure
- Stimulants have a clinically insignificant effect on blood pressure in treated, normotensive adults

Pharmacologic Treatments for ADHD

**Primary Agents**
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- α adrenergic agonists

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**Adjunctive agents**
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Atomoxetine: Mechanism of Action

Atomoxetine: Mechanism of Action

- Posterior Attention System
  - Increased NE
    - Improved alerting and orienting
    - Reduced “startle” and over-reactivity
- Anterior Attention System
  - Increased NE and DA
    - Improved focusing
    - Improved executive functioning

DA = dopamine; NE = norepinephrine.
Atomoxetine: Effects on Dopamine

• Downstream increase in DA activity in the prefrontal cortex
  – Consistent with improved executive functioning
• No increase in DA activity in the nucleus accumbens
  – Not associated with abuse liability
• No increase in DA in the striatum
  – Not associated with motor activity (tics)

Atomoxetine: Side Effects

- Dizziness, high blood pressure
- Headache, irritability, nervousness
- Abdominal pain, nausea, vomiting, loss of appetite, weight loss
- Dry mouth, constipation, urinary hesitancy
- Decreased sexual desire
- Very slight chance of hepatic insufficiency
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α₂-Adrenergic Agonists
(Clonidine, Guanfacine)

- Mechanism of action: partial agonist of NE
- Decreases erratic activity of locus coeruleus
- Increases neurotransmission in prefrontal cortex
- First introduced as anti-hypertensive agents
- Helpful for patients who are highly aroused, impulsive, emotionally labile, irritable and explosive
- Reduces anxiety, defiance, and aggression
- Useful in controlling tics

Guanfacine: How does it work?

Stimulation of α2A-adrenergic receptors

- Inhibits cAMP production which closes nearby HCN channels
- Increases pyramidal excitability
- Strengthens connectivity of DLPFC microcircuits
- Reduces distractibility and improves working memory in monkeys and humans
- Enhances DLPFC perfusion in monkeys during working memory tasks

HCN = hyperpolarization-activated cyclic nucleotide-gated channels
α₂-Adrenergic Agonists: Side Effects (Clonidine, Guanfacine)

- Sedation, fatigue
- Dizziness
- Dry mouth, indigestion, nausea
- Nightmares, insomnia
- Anxiety, depression
- Hypertensive crisis with sudden discontinuation

α₂-Adrenergic Agonists: Dosing (Clonidine, Guanfacine)

- Start with ½ tablet at bedtime (0.05 mg clonidine, 0.5 mg guanfacine)
- Add ½ tablet in the morning as tolerated (5–15 days)
- Continue incremental increases by ½ tablet q weekly
- Titrate upwards as tolerated to maximum of 0.4/4 mg daily
- Extended-release preparation is approved for children and adolescents; need to increase dose by 33%

Combining Agents

- Stimulants may be combined with atomoxetine when patients do not respond adequately to either medication alone.
- Clinical trials have been conducted on the following combination therapies:
  - Atomoxetine and MPH
  - Clonidine and MPH
  - Guanfacine and MPH

Managing Inadequate Response

- Newly diagnosed patients may take 2 to 3 months to be stabilized on medication
- Adjust the dose or consider switching medications
- Ensure that comorbid conditions are treated
- Try combination treatment
- Manage side effects
- Reconsider the diagnosis and possible presence of confounding comorbid psychiatric conditions

Non-Stimulants in Development

- Dasotraline - DNRI
- Mazindol CR - TRI + Orexin
- Fasoracetam NFC1 - mGluR activator*
- Centanafadine - TRI
- Viloxazine – NRI

*gene mutation predicts response
Dasotraline Pediatric ADHD Study

6–12 years olds, rated on home version of ADHD-RS
Intent to treat analysis
Adverse event discontinuation rate: 2mg: 6.3%, 4 mg: 13%, Placebo: 1.7%

Goldman R, et al. APSARD, 2017
Dasotraline for ADHD in Adults: RCT Proof of Concept Trial

Inhibits Dopamine and Norepinephrine Transporters more than Serotonin

- N=331 with post baseline efficacy assessment
- Discontinuation due to adverse events: 10.3% (4 mg), 27.8% (8 mg), and 1.8% (placebo)

Koblan et al., Neuropsychopharm, 2015
Mazindole-CR for Adult ADHD: TRI Plus Orexin Modulation

Effect Size=1.09

Wigal et al. CNS Drugs March 2018
https://doi.org/10.1007/s40263-018-0503-y
Comparative Analysis of 9-Gene/CNTN4 Subset from the SAGA Trial: ∆ in ADHD RS

SAGA
Change in ADHD-RS (N=96)

SAGA 9-Gene Subset
Change in ADHD-RS (n=42)

Elia, J. et al, Glutamatergic network gene mutations in children and adolescents with ADHD. Poster presented at: 6th World Congress on ADHD; April 21, 2017; Vancouver, Canada
THANK YOU!!

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