Disclosure
I have no conflicts of interests to disclose
No affiliations or financial disclosures with pharmaceutical manufacturers
Off-label use of drugs will be discussed

Objectives
Recognize the underlying pathophysiology of ADHD
Identify the signs and symptoms of ADHD and its subtypes
Compare and contrast the pharmacological classes used to treat ADHD
Interpret the study results of the MTA and PATS study
Discuss the effects on long-term stimulant medication use
ADHD is not a real disorder

History of ADHD and Stimulants

1902 - British Pediatrician, Sir George Frederic Still, first describes "abnormal defect of moral control in children" in scientific literature

1952 - Diagnostic and Statistical Manual of Mental Disorders (DSM) issued by the American Psychiatric Association (APA)

1955 - Methylphenidate first patented by Novartis and approved by the FDA for hyperactivity

1987 - Attention Deficit Hyperactivity Disorder (ADHD) officially recognized by the APA

2002 - First non-stimulant drug approved for ADHD by the FDA

Attention Deficit Hyperactivity Disorder

- Inattention
- Impulsivity
- Interference

- Academic
- Family
- Social
Worldwide...

5-6% of children


In the United States...

5,000,000

10%

Pediatric patients ages 3-17

ADHD & Comorbidities

Percentage of children with ADHD and another disorder


64%
52%
33%
17%
13%
1%

In the United States...


Prevalence between males versus females

2 : 1
Risk Factors

Psychosocial
Disordered family organization

Biological toxins
Polychlorinated biphenyls (PCBs)
Lead

High levels of sugar
Not supported by evidence; concern for oral health and endocrine disorders

Pregnancy and Delivery
Fetal distress, maternal age, low birth weight, prematurity, anemia, hemorrhage, carcinogenic exposure

Iron & Zinc deficiencies

Genetics contributory to development of ADHD

Smartphones and Attention

Limited empirical evidence suggests either endogenous or exogenous mobile phone engagement impairs acute cognitive task performance.

Evidence for long-term impact has yet to be determined.

More likely associated with poor sleeping habits contributing to day-time sleepiness and fatigue.

Conclusion: Educate parents and children on allowing adequate time to disconnect especially before bedtime.

Wilmer HH, Sherman LE, Chein JM. Front Psychol. 2017;8:605.
**Media Use in Children**

**American Academy of Pediatrics Recommendations**

For children younger than 18 months, avoid use of screen media other than video-chatting.

For children ages 2 to 5 years of age, limit screen use to 1 hour per day of high-quality programs.

For children ages 6 and older, place consistent limits on the time spent using media, types of media, and avoid disruption in adequate sleep, physical activity, and other behaviors.

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**Pathophysiology**

Dysregulation in dopamine
- Anterior circuitry
- Higher executive decision

Dysregulation in norepinephrine
- Posterior circuitry
- Thalamus
- Cerebellum

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**Structural Abnormalities**

Neuroimaging findings demonstrated areas with largest volumetric reductions:
- Cerebellar vermis
- Corpus callosum
- Right caudate
- Total cerebral volume

Loss of functionality in gray and white matter; **DECREASED** cortical thickening

Deficit in cognitive processing, attention, motor planning of processing
Functional Abnormalities

fMRI demonstrated hypoactivity in frontal regions of the brain
- Anterior cingulate
- Dorsolateral prefrontal cortex
- Inferior prefrontal cortex
- Orbitofrontal cortex

Spontaneous low-frequency activity as the DEFAULT

Deficit in performance in daily tasks

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Positron Emission Tomography (PET) scan

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Diagnosis & Evaluation

Diagnostic and Statistical Manual of Mental Disorders (DSM), Fifth edition categorizes ADHD into three subtypes

- Inattentive
- Hyperactivity-Impulsiveness
- Combined
Inattentive Hyperactivity-Impulsiveness

- Fails to give close attention to details or makes careless mistakes
- Difficulty sustaining attention
- Does not appear to listen
- Struggles to follow instructions
- Difficulty with organization
- Avoids or dislikes tasks requiring sustained mental effort
- Loose things
- Forgets or misplaces things

<table>
<thead>
<tr>
<th>Inattentive</th>
<th>Hyperactivity-Impulsiveness</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fidgets with hands or feet</td>
<td>Difficulty engaging in activities quietly</td>
</tr>
<tr>
<td>Difficulty remaining seated</td>
<td>Acts if driven by a motor</td>
</tr>
<tr>
<td>Runs and climbs excessively</td>
<td>Talks excessively</td>
</tr>
<tr>
<td>Difficulty engaging in activities quietly</td>
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</tbody>
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Diagnosis Criteria

Diagnostic and Statistical Manual of Mental Disorders (DSM), Fifth edition

1. Must have six or more characteristics in either subtypes (five or more in ages 17 to adults)
2. Must create significant difficulty in at least two areas of life
3. Must present before the age of 12
4. Must be present for at least 6 months
5. Symptoms not associated with another mental disorder

Clinical Practice Guideline by AAP

ADHD: Clinical Practice Guideline for the Diagnosis, Evaluation, and Treatment of Attention-Deficit/Hyperactivity Disorder in Children and Adolescents
Diagnostic Evaluation

1. Evaluate any child 4-18 years old with academic or behavioral problems with hyperactivity, impulsiveness, or inattention

1. Multi-faceted approach and evaluation necessary

ADHD Diagnosis

- Patient interview
- Patient self-reported instrument
- Academic record
- Administrative reports
- Validated ADHD instrument
- Medical history
- Family history
- History of symptoms
- Family history
- Social history
- Physical exam
- Clinician observations
Diagnostic Evaluation

1. Evaluate any child 4-18 years old with academic or behavioral problems with hyperactivity, impulsiveness, or inattention

1. Multi-faceted approach and evaluation necessary

1. Rule-out alternative causes and look for coexisting conditions

1. Diagnosis confirmed based on DSM-V criteria

Alternative causes

1. Emotional or behavioral
   a. Anxiety, depression, oppositional defiance

1. Developmental
   a. Learning milestones, language barriers

1. Physical
   a. Neurotrauma, sleep disorders, sleeping habits, substance abuse, tonsillitis
Algorithm demonstrated higher quality of care for in ADHD diagnoses

Treatment Recommendations

<table>
<thead>
<tr>
<th>AACAP</th>
<th>AAP</th>
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</thead>
<tbody>
<tr>
<td><strong>1st</strong></td>
<td>Stimulant</td>
</tr>
<tr>
<td><strong>2nd</strong></td>
<td>Atomoxetine (Strattera®)</td>
</tr>
<tr>
<td><strong>3rd</strong></td>
<td>Review diagnosis; consider behavior therapy</td>
</tr>
<tr>
<td><strong>4th</strong></td>
<td>Bupropion, TCAs, alpha-2-agonist</td>
</tr>
</tbody>
</table>

National Institute of Mental Health
The Multimodal Treatment of Attention Deficit Hyperactivity Disorder Study (MTA)

Multicenter randomized, placebo-controlled study designed to evaluate leading treatments for ADHD

MTA study followed time period up to 14 months

**Compared four distinct treatment strategies**
1. Medication management
2. Behavioral therapy
3. Combination of medication management and behavioral therapy
4. Usual community care

**Conclusion**
14 months
1. All groups showed improvement over baseline
2. Medication management and combination group showed statistically significant improvement

3 years
1. All groups showed improvements over baseline
2. No statistically significant differences in groups
National Institute of Mental Health
The Multimodal Treatment of Attention Deficit Hyperactivity Disorder Study (MTA)

Conclusion

8 years
1. Type or intensity of 14 month treatment does NOT predict function six-to-eight years later
2. Severity of ADHD, conduct problems, social advantages, and response to treatment more likely predictive of function


National Institute of Mental Health
The Preschool ADHD Treatment Study (PATS)

Conclusion

1. Lower doses utilized overall in PATS study
2. Demonstrated association of side effects at higher doses
3. Initiating stimulants in this population required very close monitoring


National Institute of Mental Health
The Preschool ADHD Treatment Study (PATS)

Conclusion

6 years
1. Approximately 80% of children initially diagnosed with ADHD, who mostly received parent training and controlled medication treatment, continued to be diagnosed with ADHD in mid-to-late childhood
2. Medication status, on versus off, did not predict symptom severity change from year 3 to year 6
3. Greater efforts needed to develop more effective ADHD intervention strategies

Stimulants

1. First line treatment for ADHD in children > 6 years of age

1. Selection based on Pharmacodynamic and Pharmacokinetic profile
   a. Dosing
   b. Duration of action
   c. Administration
   d. Adverse effects
   e. Cost

Titration

1. Dose increase every 3-7 days depending on tolerability

1. Titration process can last up to 3 months

1. Optimal dose is highly dependent on the patient

1. Pharmacist intervention by helping prescribers understand the logistics of quantity prescribed

Pharmacology of Stimulants

Methylphenidate

Dopamine and Norepinephrine reuptake inhibitor; resulting in higher concentrations of DA and NE in the synaptic cleft
Pharmacology of Stimulants

Amphetamines

Dopamine and Norepinephrine reuptake inhibitor
Stimulates release of monoamines (at higher doses)
Inhibits monoamine oxidase

Methylphenidate

1. Gold standard, most extensively researched and studied
1. Short, intermediate, and long-acting preparations available
1. Multiple formulations available

Methylphenidate immediate-release - Ritalin®, Methylin®
Methylphenidate long-acting - Ritalin LA®
Methylphenidate extended-release - Methylin ER®, Quillivant XR®,
Methylphenidate extended-release - Concerta®,
Methylphenidate transdermal patch - Daytrana®

Methylphenidate extended-release (Concerta®)

Osmotic controlled-release oral delivery system (OROS®)
Trilayer core surrounded by a semipermeable membrane with an immediate-release drug overcoat
22% of drug is immediate-release
78% of drug is extended-release
Methylphenidate extended-release (Concerta®)

![Graph showing plasma concentration over time for Concerta® and methylphenidate 5 mg tid.]

Methylphenidate extended-release (Quillivant XR®)

Delayed release mechanism via proprietary encapsulation of microspheres

Dexmethylphenidate

1. Active d-enantiomer of racemic methylphenidate
2. Dosing is one-half of racemic methylphenidate
3. Short and long-acting formulations

Dexmethylphenidate immediate release - Focalin®
Dexmethylphenidate extended release - Focalin XR®
Dexmethylphenidate extended-release - Focalin XR®

Bimodal plasma concentration-time profile
Bead-filled formulations produces two distinct peaks

Dextroamphetamine and amphetamine
1. Short and long-acting formulations available
1. One of the most commonly abused stimulants

Dextroamphetamine/Amphetamine immediate-release - Adderall®
Dextroamphetamine/Amphetamine extended-release - Adderall XR®
Lisdexamfetamine dimesylate - Vyvanse®

Lisdexamfetamine dimesylate (Vyvanse®)
Prodrug converted by enzymatic activity mediated only in the bloodstream

Designed to minimize abuse potential
Stimulant Adverse Effects

**Black-box warning**: Misuse may cause sudden death and serious cardiovascular events

Kaland et al.
1. Most common reason was either exploratory in nature (93.4%) and therapeutic error (65.6%) in children < 6 years of age
2. In adolescents and adults, suicide attempts (28.4%) and abuse (19.5%) 3. Major/Death outcomes (21.2%) in lisdexamfetamine group 4. Major/Death outcomes (24.7%) in dextroamphetamine/amphetamine group


Stimulant Adverse Effects

**Common**
1. Nausea
2. Loss of appetite
3. Insomnia
4. Headaches
5. Abdominal pain
6. Emotional lability

**Severe**
1. Cardiovascular (hemodynamic instability)
2. Peripheral vasculopathy (Raynaud’s phenomenon)
3. Worsening of psychiatric disorders (anxiety, agitation, increased psychomotor drive, suicidal ideation)
4. Drug-drug interaction with MAO inhibitor use
Patient Counseling - oral tablets & capsules

Medication guide must be dispensed and instruct patient/caregiver to read it

Encourage follow-up with pediatrician for blood pressure, heart rate, height and weight

Observe for changes in sleeping habits and sleep architecture; consult with pediatrician if worsened

As with many extended release products; do NOT break, crush, or chew formulations

Vyvanse® may be mixed with water, yogurt, juice; take right away

Patient Counseling - transdermal patch

Patch placement must alternate between left and right side of hip

Hold patch on skin for 30 seconds and smooth down edges

Remove after 9 hours to allow child to obtain restful sleep

Be mindful when discarding; accidental placement on smaller children can be lethal
Non-Stimulants

Consider first line for patients with risk of substance abuse or diversion
Less risk for changes in sleep habits and architecture; less risk of appetite suppression
Risk for worsening psychiatric disorders remain; suicidal ideations
Atypical antipsychotics and antidepressants have been researched; none are FDA approved for ADHD

Atomoxetine (Strattera®)

Mechanism of action: selective norepinephrine reuptake inhibitor
Black-box warning: risk of suicidal ideation; monitor for suicidal behavior
Adverse effects: headache, insomnia, somnolence, dry mouth, nausea, severe hepatotoxicity within 120 days of initiation
Notes:
1. Greatest effect shown at 6 weeks; effects can be observed 1 week out
2. Do not open capsule; drug is an irritant

Guanfacine (Intuniv®)

Mechanism of action: central α2-adrenergic receptor agonist; prevents the release of norepinephrine from the presynaptic neuron
Adverse effects: somnolence, dizziness, cardiovascular effects (orthostasis, bradycardia, hypotension), skin rash (discontinue drug immediately)
Notes:
1. Do not crush
2. May be used as monotherapy or in combination with stimulants
3. Substrate for CYP3A4 metabolism; mindful on drug dosing
Clonidine (Kapvay®)

**Mechanism of action:** central α₂-adrenergic receptor agonist; prevents the release of norepinephrine from the presynaptic neuron

**Adverse effects:** headache, somnolence, dizziness, rebound hypertension (if abruptly discontinued)

**Notes:**
1. Do not crush
2. May be used as monotherapy or in combination with stimulants
3. Discontinuation requires taper for dose decrease

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Discontinuing and Re-initiation

MTA study demonstrated patients continued to improve at 3 years despite discontinuation

Drug holidays can be considered a tool used by clinicians to allow patients to:
1. Recover appetite
2. Positive impact on growth
3. Reduction in adverse effects

Re-evaluation to start medications again

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Patient Case

**History of present illness**

The mother of a healthy 8-year-old boy is concerned about his school performance. At the last parent–teacher conference, his teacher noted that he is easily distracted and routinely fails to complete both homework assignments and classroom papers. His mother states that at home he also has difficulty in completing tasks and he fidgets constantly. Although the child is very talkative, he does not answer questions clearly. His physical examination is significant only for fidgeting.
Identify signs and symptoms of ADHD

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Patient Case

Which of the following is true about the diagnosis of ADHD?

A. Symptoms must present before 18 years of age
B. Symptoms must be present for at least 6 months
C. Signs and symptoms must hinder every aspect of daily life
D. All of the states are true
Patient Case

What medication(s) would most likely be initiated first for this patient?

A. Clonidine  
B. Atomoxetine  
C. Methylphenidate  
D. Dextroamphetamine  
E. C or D

Patient Case

Brandon Stark recently started on dextroamphetamine/amphetamine 10 mg PO BID. He experienced severe nausea and decreased appetite after the first week of starting. He experiences no relief in ADHD symptoms. What is the most appropriate next step in therapy?

A. Continue dextroamphetamine/amphetamine due to delayed response  
B. Discontinue dextroamphetamine/amphetamine and initiate guanfacine  
C. Discontinue dextroamphetamine/amphetamine and initiate atomoxetine  
D. Discontinue dextroamphetamine/amphetamine and initiate methylphenidate
Patient Case

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Attention Deficit Hyperactivity Disorder

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