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**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

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**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

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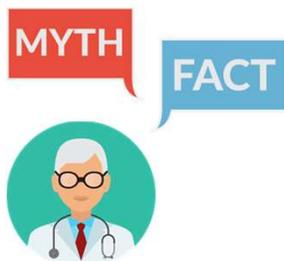
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### ADHD is not a real disorder



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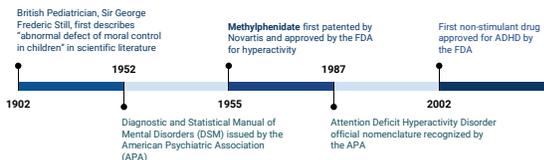
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### History of ADHD and Stimulants



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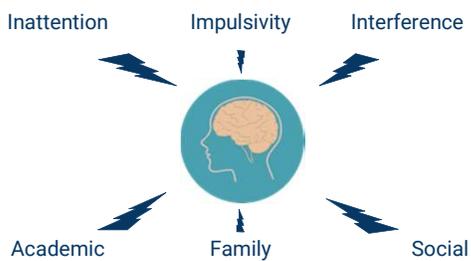
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### Attention Deficit Hyperactivity Disorder



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Worldwide...



**5-6% of children**

American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders Fifth Edition (DSM-5) 2013.

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Worldwide...



**129,000,000**

American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders Fifth Edition (DSM-5) 2013.

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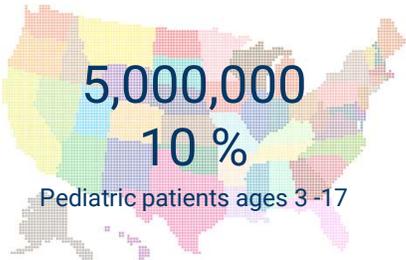
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In the United States...



**5,000,000**  
**10 %**  
Pediatric patients ages 3-17

American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders Fifth Edition (DSM-5) 2013.

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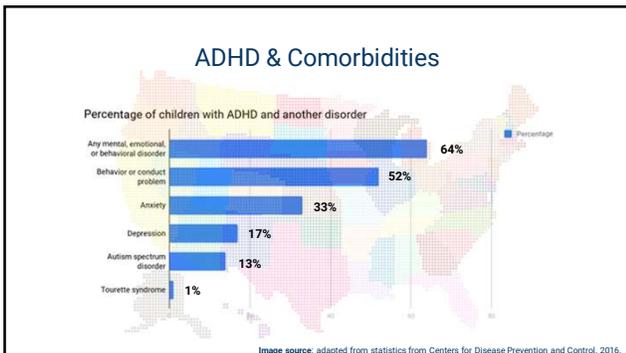
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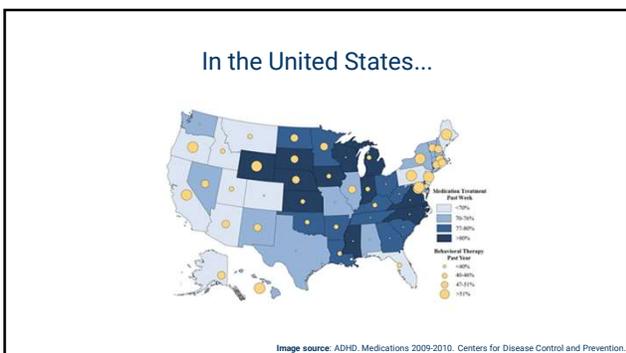
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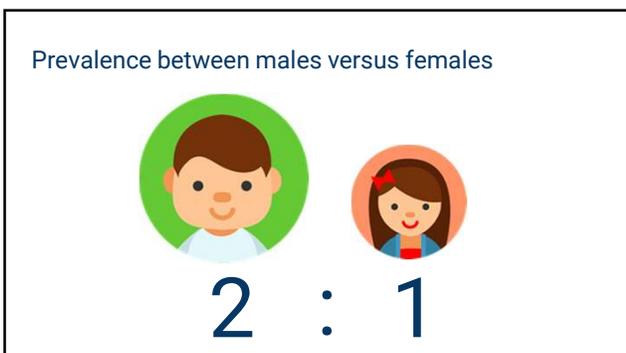
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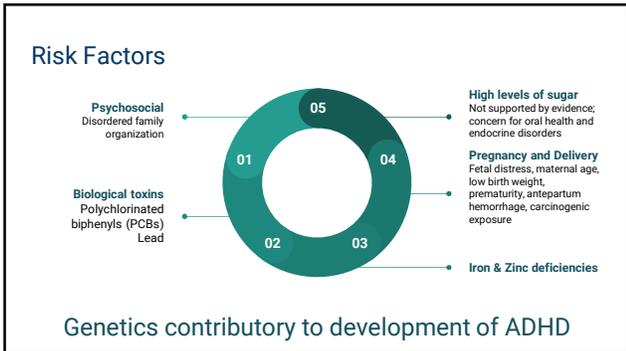
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### Smartphones and Attention

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.

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## 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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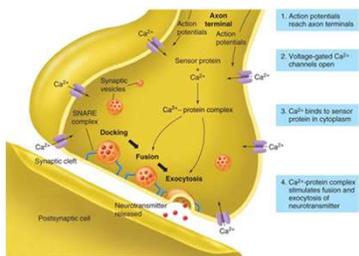
## Pathophysiology

### Dysregulation in dopamine

- Anterior circuitry
- Higher executive decision

### Dysregulation in norepinephrine

- Posterior circuitry
- Thalamus
- Cerebellum



Cortese S. Eur J Paediatr Neurol. 2012

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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

Cortese S. Eur J Paediatr Neurol. 2012

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### 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

Cortese S. Eur J Paediatr Neurol. 2012

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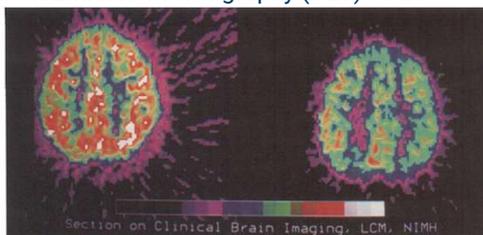
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### Positron Emission Tomography (PET) scan



Section on Clinical Brain Imaging, LCM, NIMH  
Figure. A comparison of positron emission tomography (PET) images of a patient with ADHD (right image) and a control subject (left image). The transverse section shows the frontal cortex at the bottom and the occipital cortex at the top. The colors white, red, and orange represent greater glucose metabolism while blue, green, and purple signify comparatively lower glucose metabolism. Their comparison suggests lower glucose metabolism in the frontal lobes of the ADHD subject. (Reprinted with permission from Zametkin and Hollman, N Engl J Med, 1989, 321:1218-1219.)

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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

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Inattentive	Hyperactivity-Impulsiveness
Fails to give close attention to details or makes careless mistakes	Fidgets with hands or feet
Difficulty sustaining attention	Difficulty remaining seated
Does not appear to listen	Runs and climbs excessively
Struggles to follow instructions	Difficulty engaging in activities quietly
Difficulty with organization	Acts if driven by a motor
Avoids or dislikes tasks requiring sustained mental effort	Talks excessively
Loses things	Blurts out answers before question is completed
Forgetful of daily activities	Interrupts or intrudes upon others

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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

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**Clinical Practice Guideline by AAP**

American Academy of Pediatrics  FROM THE AMERICAN ACADEMY OF PEDIATRICS  
DEDICATED TO THE HEALTH OF ALL CHILDREN™ Guidance for the Clinician in Rendering Pediatric Care

CLINICAL PRACTICE GUIDELINE

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

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### Diagnostic Evaluation

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

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### 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

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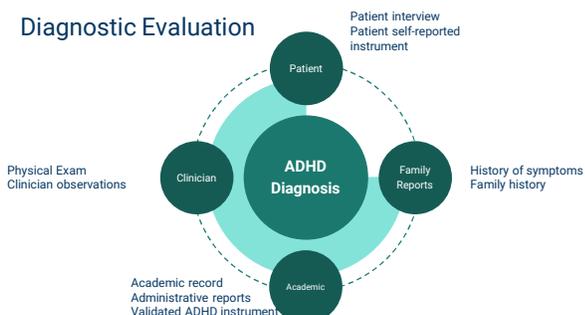
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### Diagnostic Evaluation



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**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

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**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

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**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

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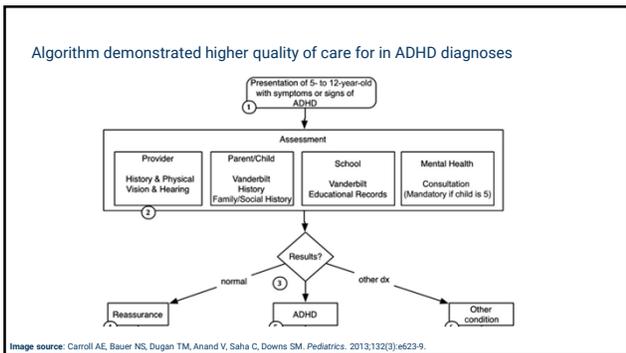
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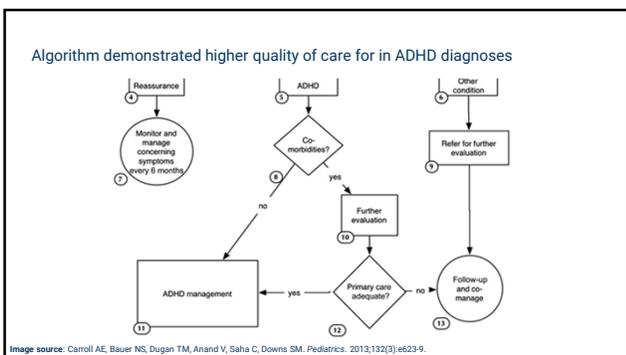
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Treatment Recommendations

**PEDIATRICS**  
OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

**Journal of the American Academy of Child & Adolescent Psychiatry**

Clinical Practice Guideline: Diagnosis and Evaluation of the Child With Attention-Deficit/Hyperactivity Disorder  
Committee on Quality Improvement, Subcommittee on Attention-Deficit/Hyperactivity Disorder  
*Pediatrics* 2000;105:1158

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Treatment Recommendations		AACAP	AAP
1 <sup>st</sup>	Stimulant		Age 4-5: Behavioral psychosocial therapy Age > 6: Stimulant x 2
2 <sup>nd</sup>	Atomoxetine (Strattera®)		Age 4-5: Stimulant x 2 Age > 6: Atomoxetine (Strattera®); Guanfacine XR (Intuniv®); Clonidine (Kapvay®)
3 <sup>rd</sup>	Review diagnosis; consider behavior therapy		
4 <sup>th</sup>	Bupropion, TCAs, alpha-2-agonist		

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**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



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

**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

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### 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

Molina BS, Hinshaw SP, Swanson JM, et al. J Am Acad Child Adolesc Psychiatry. 2009;48(5):484-500

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### National Institute of Mental Health

The Preschool ADHD Treatment Study (PATS)

Multicenter randomized, placebo-controlled study designed to evaluate short-term (5 weeks) efficacy and long-term (40 weeks) safety of methylphenidate (MPH) in preschoolers with ADHD

MTA study followed time period up to 70 weeks

#### 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




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### 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 inot 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

Riddle MA, Yershova K, Lazzaretto D, et al. J Am Acad Child Adolesc Psychiatry. 2013;52(3):264-276.e2

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**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

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**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

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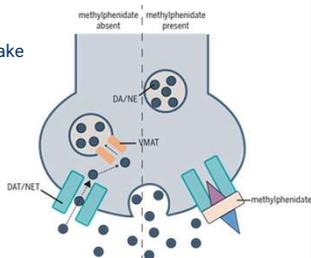
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**Pharmacology of Stimulants**

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




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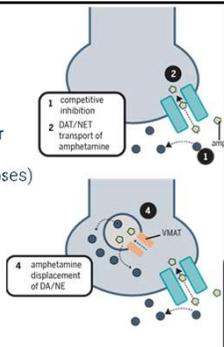
## Pharmacology of Stimulants

### Amphetamines

Dopamine and Norepinephrine reuptake inhibitor

Stimulates release of monoamines (at higher doses)

Inhibits monoamine oxidase




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## 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**®

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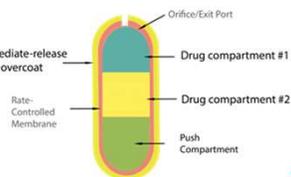
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## Methylphenidate extended-release (Concerta®)

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




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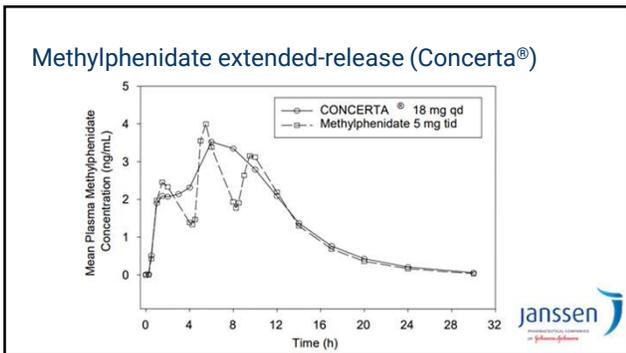
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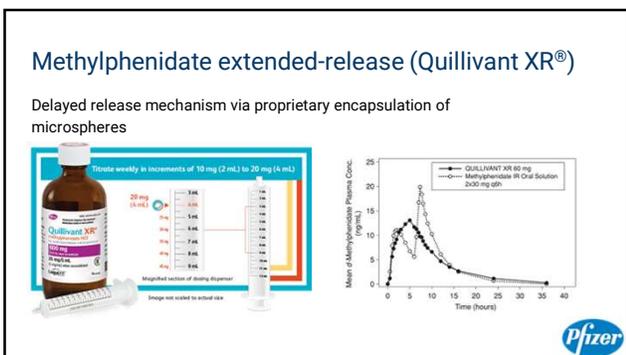
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### Dexmethylphenidate



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

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

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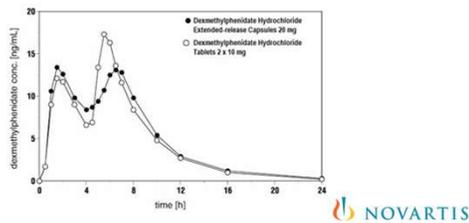
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### Dexmethylphenidate extended-release - Focalin XR®

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




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### 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®**




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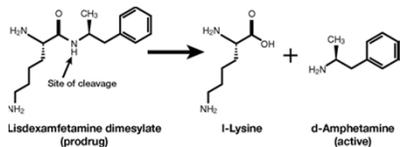
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### Lisdexamfetamine dimesylate (Vyvanse®)

Prodrug converted by enzymatic activity mediated only in the bloodstream



Designed to **minimize abuse potential**




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Lisdexamfetamine dimesylate (Vyvanse®)

**7 CAPSULE STRENGTHS\***



**\*The amount of powder in a Vyvanse capsule varies by capsule strength.**

**6 CHEWABLE TABLET STRENGTHS**





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**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

Kaland ME, Klein-schwartz W. Clin Toxicol. 2015;53(5):477-85.

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**Stimulant Adverse Effects**

**Common**

1. Nausea	4. Headaches
2. Loss of appetite	5. Abdominal pain
3. Insomnia	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

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Patient Counseling - oral tablets & capsules



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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

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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

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### 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

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### 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



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### Guanfacine (Intuniv®)

**Mechanism of action:** central  $\alpha_2A$ -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



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### Clonidine (Kapvay®)

**Mechanism of action:** central  $\alpha_{2A}$ -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

Ibrahim K, Donyal P. J Atten Disord. 2015;19(7):551-68

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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.

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Patient Case

Identify signs and symptoms of ADHD

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.

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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

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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

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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

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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

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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

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### 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

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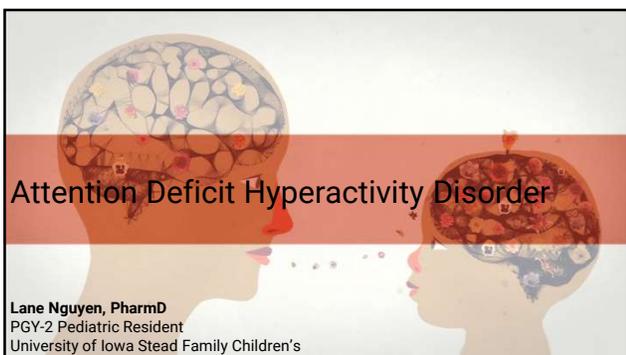
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