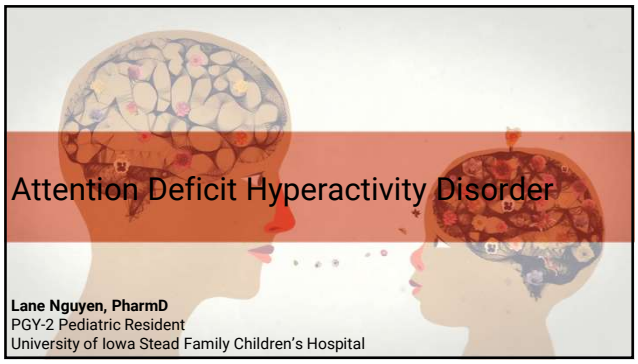


Attention Deficit Hyperactivity Disorder

Lane Nguyen, PharmD
PGY-2 Pediatric Resident
University of Iowa Stead Family Children's Hospital

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

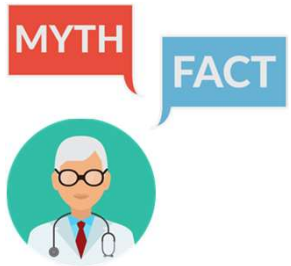
Identify the signs and symptoms of ADHD and its subtypes

Compare and contrast the pharmacological classes used to treat ADHD

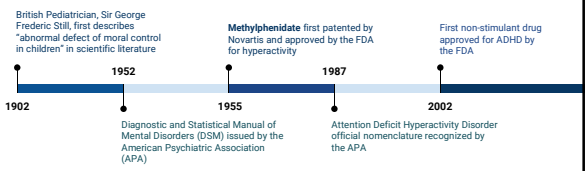
Interpret the study results of the MTA and PATS study

Discuss the effects on long-term stimulant medication use

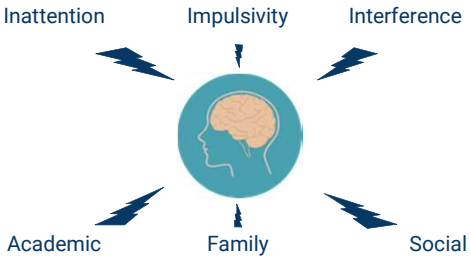
ADHD is not a real disorder



History of ADHD and Stimulants



Attention Deficit Hyperactivity Disorder



Worldwide...

5-6% of children

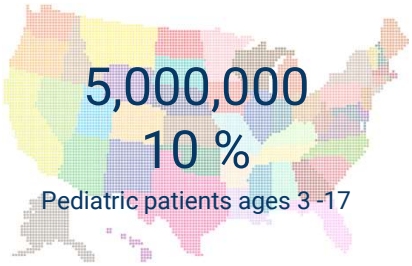
American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*.Fifth Edition (DSM-5).2013.

Worldwide...

129,000,000

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

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.

ADHD & Comorbidities

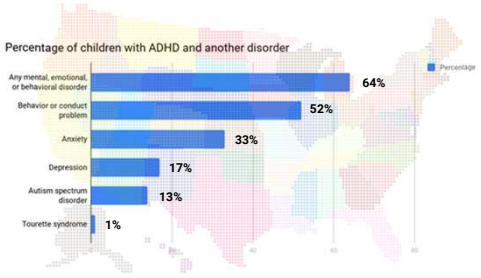


Image source: adapted from statistics from Centers for Disease Prevention and Control. 2016.

In the United States...

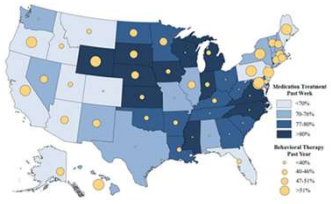
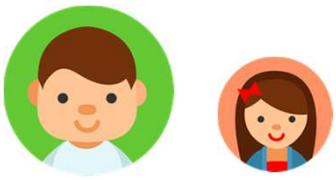


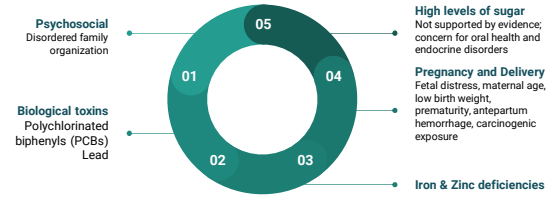
Image source: ADHD. Medications 2009-2010. Centers for Disease Control and Prevention.

Prevalence between males versus females



2 : 1

Risk Factors



Genetics contributory to development of ADHD

Smartphones and Attention

Image source:
IPhone X. Courtesy of Apple, Inc
Galaxy S9+. Courtesy of Samsung electronics.

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

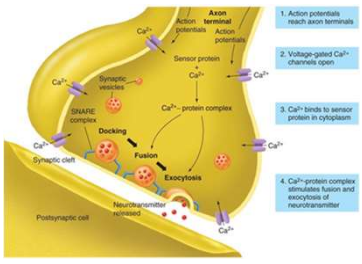
For children ages **2 to 5 years of age**, limit screen use to 1 hour per day of high-quality programs

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

Pathophysiology

Dysregulation in **dopamine**
- Anterior circuitry
- Higher executive decision

Dysregulation in **norepinephrine**
- Posterior circuitry
- Thalamus
- Cerebellum



Cortese S. *Eur J Paediat Neurol.* 2012

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 Paediat Neurol.* 2012

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 Paediat Neurol.* 2012

Positron Emission Tomography (PET) scan

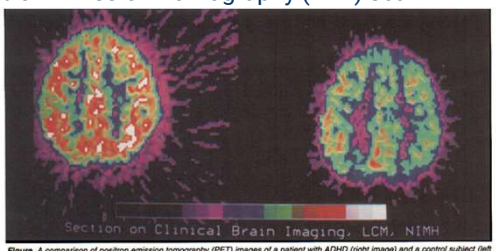


Figure. *A comparison of positron emission tomography (PET) images of a patient with ADHD (right image) and a control subject (left image). The transverse section shows the frontal cortex at the bottom and the occipital cortex at the top. The colors white, red, and orange represent greater glucose metabolism 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 colleagues, N Engl J Med. 1990;323:1415-1415.)*

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	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

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

American Academy of Pediatrics
DEDICATED TO THE HEALTH OF ALL CHILDREN™

FROM THE AMERICAN ACADEMY OF PEDIATRICS
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

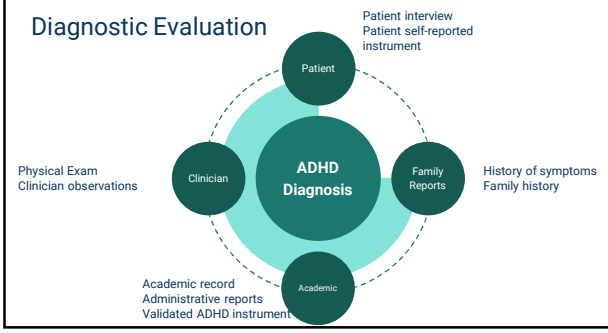
Diagnostic Evaluation

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

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

Diagnostic Evaluation



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

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

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

Algorithm demonstrated higher quality of care for in ADHD diagnoses

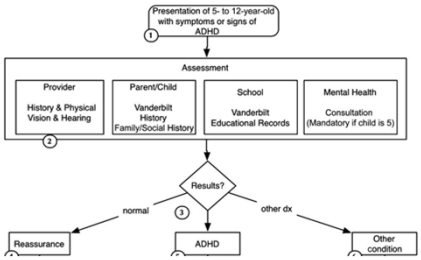


Image source: Carroll AE, Bauer NS, Dugan TM, Anand V, Saha C, Downs SM. *Pediatrics*. 2013;132(3):e623-9.

Algorithm demonstrated higher quality of care for in ADHD diagnoses

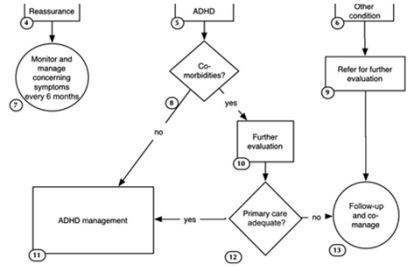


Image source: Carroll AE, Bauer NS, Dugan TM, Anand V, Saha C, Downs SM. *Pediatrics*. 2013;132(3):e623-9.

Treatment Recommendations

Journal of the American Academy of Child & Adolescent Psychiatry

PEDIATRICS
OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

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

Treatment Recommendations

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

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

NIH National Institute of Mental Health

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

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

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

NIH National Institute of Mental Health

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):264-278.e2.

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

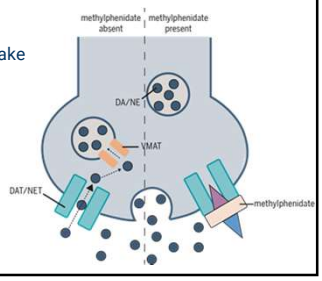
1. Titration process can last up to 3 months

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

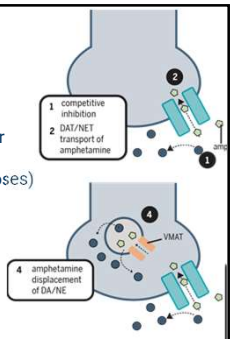


Pharmacology of Stimulants

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

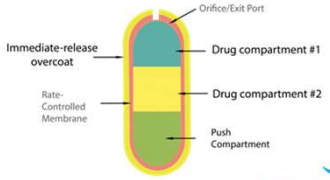
Methylphenidate immediate-release - **Ritalin®, Methylin®**
Methylphenidate long-acting - **Ritalin LA®**
Methylphenidate extended-release - **Methylin ER®, Quillivant XR®,**
Methylphenidate extended-release - **Concerta®**
Methylphenidate transdermal patch - **Daytrana®**

Methylphenidate extended-release (Concerta®)

Osmotic controlled-**r**elease **o**ral delivery **s**ystem (**OROS®**)

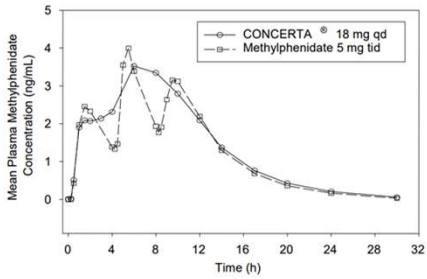
Trilayer core surrounded by a semipermeable membrane with an **immediate-release** drug overcoat

22% of drug is immediate-release
78% of drug is extended-release



janssen

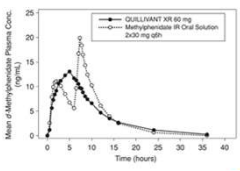
Methylphenidate extended-release (Concerta®)



janssen

Methylphenidate extended-release (Quillivant XR®)

Delayed release mechanism via proprietary encapsulation of microspheres



Pfizer

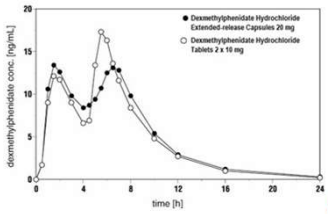
Dexmethylphenidate

1. Active d-enantiomer of racemic methylphenidate
1. Dosing is one-half of racemic methylphenidate
1. 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



NOVARTIS

Dextroamphetamine and amphetamine

II

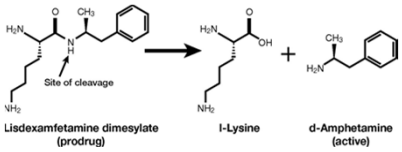
1. Short and long-acting formulations available
1. One of the most commonly abused stimulants

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

Shire
To be as brave as the people we help

Lisdexamfetamine dimesylate (Vyvanse®)

Prodrug converted by enzymatic activity mediated only in the bloodstream



Designed to **minimize abuse potential**

Shire
To be as brave as the people we help

Lisdexamfetamine dimesylate (Vyvanse®)

Shire
To be as brave as the people we help

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.

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

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 α_{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

Clonidine (Kapvay®)

Mechanism of action: central α_{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

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, Donyai P. *J Atten Disord.* 2015;19(7):551-68.

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.

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.

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

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

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

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
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D. Discontinue dextroamphetamine/amphetamine and initiate methylphenidate