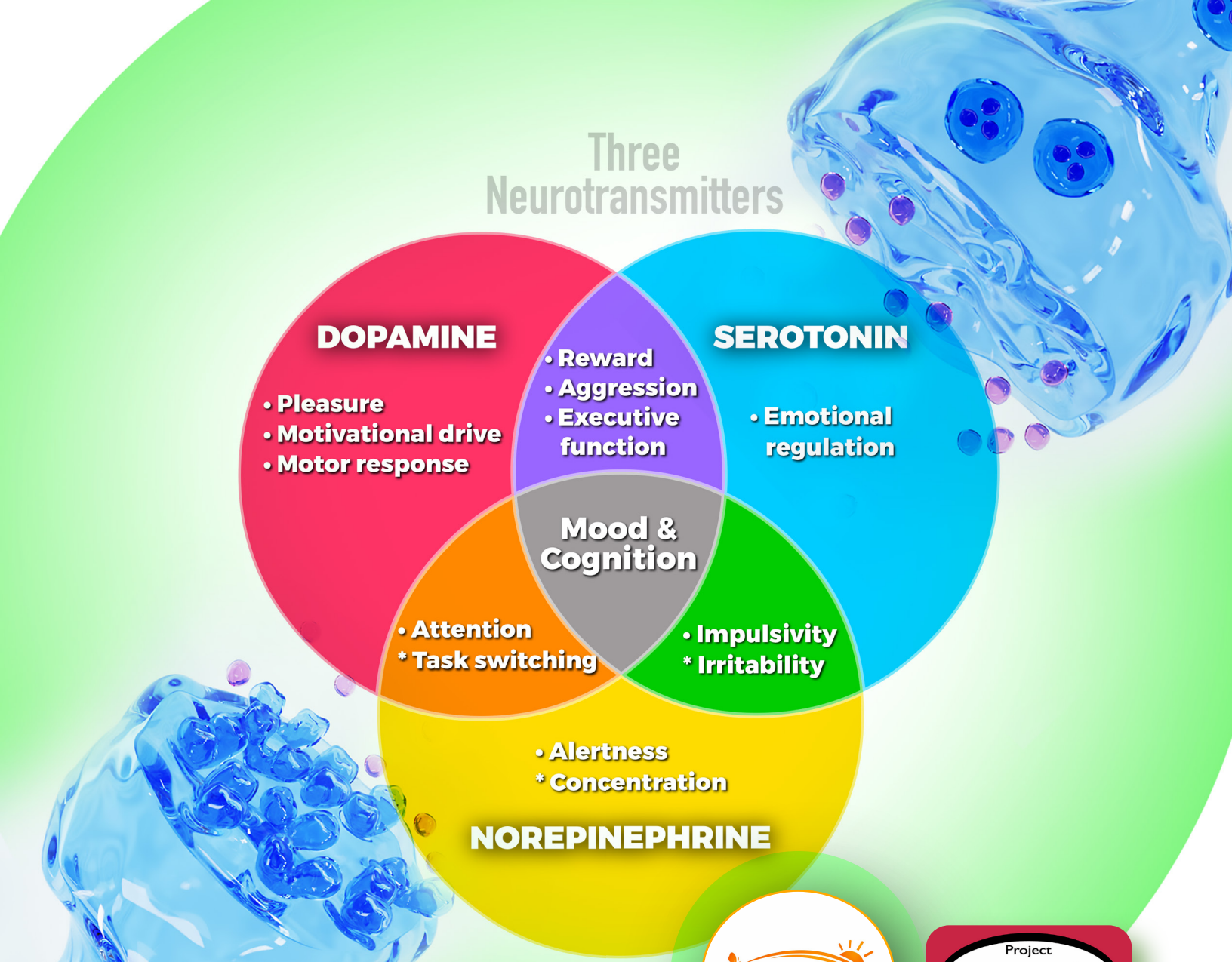


REFRAMING ADHD:

From Full Clinical Presentation to Neurobiology and Optimized Management

MED LEARNING GROUP

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PROGRAM AGENDA

I. **Introduction and Pre-Test**

II. **The Full Spectrum of ADHD: Beyond Core Symptoms to Associated Features and Lifespan Burden**

III. **The Neurobiology of ADHD: Expanding Beyond Dopamine and Norepinephrine**

IV. **Navigating Treatment Limitations and the Evolving ADHD Pharmacotherapy Landscape**

V. **Case Study Discussion**

VI. **Conclusions, Q&A, & Post-Test**

Reframing ADHD: From Full Clinical Presentation to Neurobiology and Optimized Management

Pediatric Track

PROGRAM CHAIRS
Ann Childress, MD
President, Center for Psychiatry and Behavioral Medicine
Clinical Associate Professor
Kirk Kerkorian School of Medicine at UNLV
Clinical Adjunct Associate Professor
Touro University Nevada College of Osteopathic Medicine
Las Vegas, Nevada

PROGRAM OVERVIEW

This case-based ECHO series will help clinicians confidently manage ADHD from diagnosis to treatment. We will review practical evaluation techniques and learn how to diagnose patients by identifying clinical features, comorbidities, and factors driving functional impairment. The program will detail ADHD neurobiology, specifically how dopamine, norepinephrine and serotonin interact. Finally, we will review the latest clinical evidence for both current and emerging pharmacotherapies, analyzing their strengths and limitations to help you choose the best treatment for your patients. This interactive CME program will bridge the gap between complex neuroscience and practical, evidence-based care.

TARGET AUDIENCE

These educational activities will be designed for primary care clinicians (including family medicine and internal medicine physicians), and pediatricians who diagnose and manage patients with ADHD across the lifespan.

LEARNING OBJECTIVES

Upon the completion of this program, attendees should be able to:

- Implement comprehensive evaluation techniques to identify the broader clinical features of ADHD and factors that influence functional impairment and disease burden
- Identify the neurobiological underpinnings of ADHD, including the role of and interplay between dopamine, norepinephrine, and serotonin
- Apply clinical evidence for current and emerging ADHD pharmacotherapies, including their strengths and limitations, to inform treatment selection and comprehensive disease management of ADHD

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Faculty Member	Disclosures
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Reframing ADHD: From Full Clinical Presentation to Neurobiology and Optimized Management

Ann Childress, MD

President, Center for Psychiatry and Behavioral Medicine, Inc.
Adjunct Associate Professor
Kirk Kerkorian School of Medicine
UNLV and Touro University
Las Vegas, Nevada

Disclosures

Dr Childress reports the following disclosures

- **Consulting Fees:** Aardvark Therapeutics, Axsome Therapeutics, Cingulate Inc, Corium, Zevra Therapeutics, Lumos Pharma, Neurocentria, Otsuka, Supernus, Tris Pharma
- **Advisory Board:** Alkermes, Bristol Myers Squibb, Collegium, Supernus Pharmaceuticals
- **Speakers Bureaus:** Alora, Corium, Collegium, Noven, Otsuka, Supernus, Tris Pharma
- **Contracted Research:** Aardvark Therapeutics, Alkermes, Axsome, Bristol Myers Squibb, Cingulate, Corium, Syndeio Biosciences, Collegium, Eli Lilly and Company, Lumos Pharma, Neurocentria, Noven, Otsuka, Supernus, Suven Life Sciences, Tris Pharma, Vanda
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Learning Objectives

- Implement comprehensive evaluation techniques to identify the broader clinical features of attention-deficit/hyperactivity disorder (ADHD) and factors that influence functional impairment and disease burden
- Identify the neurobiological underpinnings of ADHD including the role of and interplay between dopamine, norepinephrine, and serotonin
- Apply clinical evidence for current and emerging ADHD pharmacotherapies, including their strengths and limitations, to inform treatment selection, and comprehensive disease management of ADHD

Criteria at a Glance: ADHD

Persistent inattention and/or hyperactivity-impulsivity symptoms that interfere with functioning or development

- Must have onset of symptoms before age 12 years
  - Those aged ≤16 years must have ≥6 symptoms
  - Those aged ≥17 years must have ≥5 symptoms
- Must have impairment in social, academic, or occupational functioning
- Not better explained by another disorder



American Psychiatric Association (APA). *Diagnostic and Statistical Manual of Mental Disorders-5th edition Text Revision* (DSM-5-TR). 2022 (https://psychiatryonline.org/doi/book/10.1176/appi.books.9780890425787)

A Closer Look at ADHD

Inattention

- Misses details/makes careless mistakes
- Has difficulty sustaining attention
- Does not seem to listen
- Does not follow through
- Has difficulty organizing
- Avoids/dislikes tasks
- Loses things
- Is easily distracted
- Is forgetful

Hyperactivity

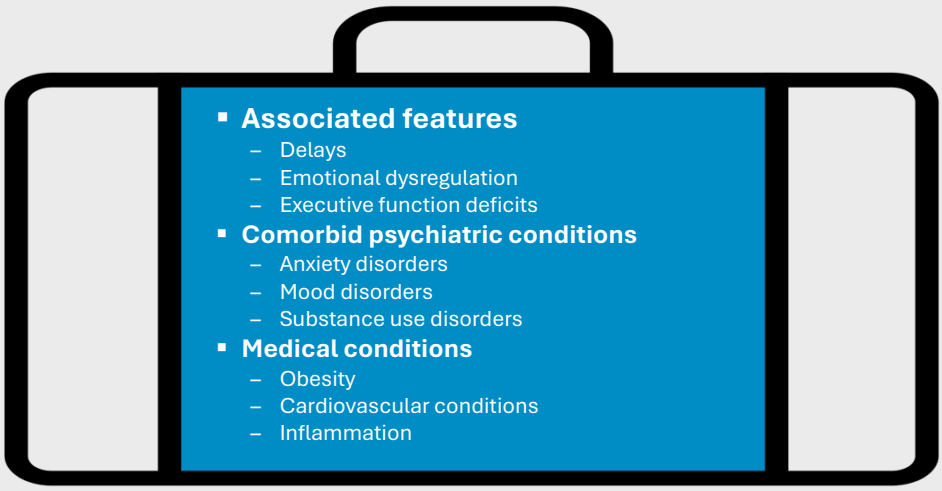
- Fidgets
- Runs about/climbs/is restless
- Has trouble sitting
- Talks excessively
- Is unable to play quietly
- Is "on the go" or "driven by a motor"

Impulsivity

- Blurts out answers
- Has difficulty waiting
- Interrupts others

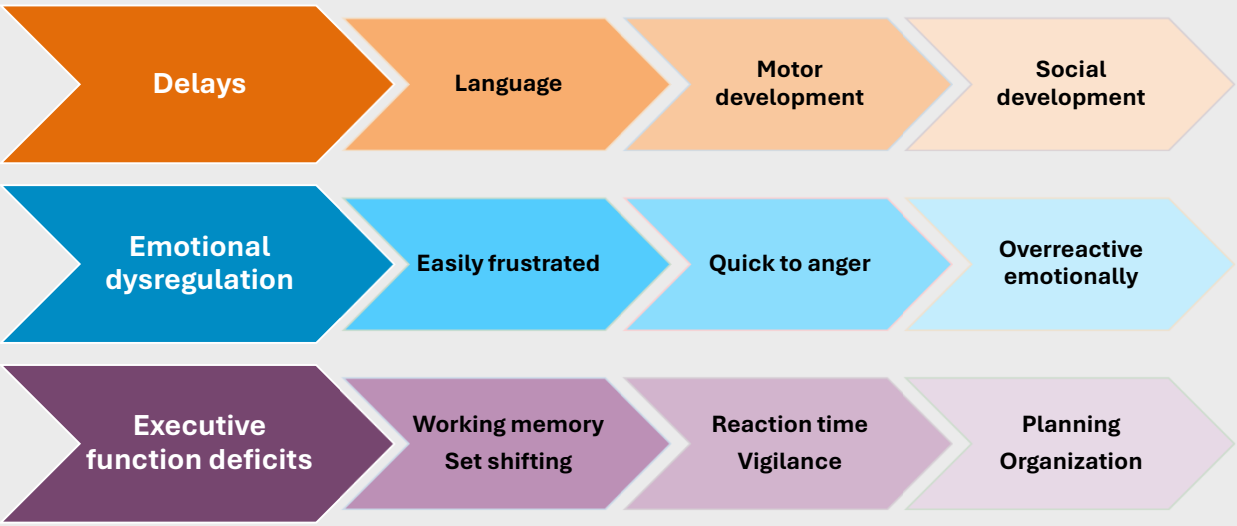
American Psychiatric Association (APA). *Diagnostic and Statistical Manual of Mental Disorders-5th edition Text Revision* (DSM-5-TR). 2022 (https://psychiatryonline.org/doi/book/10.1176/appi.books.9780890425787)

ADHD Usually Doesn't Travel Alone



American Psychiatric Association (APA). *Diagnostic and Statistical Manual of Mental Disorders-5th edition Text Revision* (DSM-5-TR). 2022 (https://psychiatryonline.org/doi/book/10.1176/appi.books.9780890425787)

ADHD Associated Features



American Psychiatric Association (APA). *Diagnostic and Statistical Manual of Mental Disorders-5th edition Text Revision* (DSM-5-TR). 2022 (https://psychiatryonline.org/doi/book/10.1176/appi.books.9780890425787)

How Common Are ADHD Associated Features?



Emotional dysregulation

- 34% to 70% of adults with ADHD
- 40% to 50% of children with ADHD



Executive function deficits

- 30% to 73% of individuals with ADHD
- 37% of those treated with stimulants continue to have deficits

American Psychiatric Association (APA). *Diagnostic and Statistical Manual of Mental Disorders-5th edition Text Revision* (DSM-5-TR). 2022 (https://psychiatryonline.org/doi/book/10.1176/appi.books.9780890425787). Faraone SV, et al. *J Child Psychol Psychiatry.* 2019;60(2):133-150. Shaw P, et al. *Am J Psychiatry.* 2014;171(3):276-293. Biederman J, et al. *J Clin Psychiatry.* 2006;67(4):524-540. Brown TE, et al. *J Atten Disord.* 2009;13(2):161-167.

Prevalence of Comorbid Psychiatric Disorders in Adults With ADHD

Anxiety disorders
3.7% to 47.1%

Major depressive disorder
2.6% to 53.8%

Bipolar disorder
0.4% to 22.7%

Substance use disorders
4.2% to 46.0%

Hartman CA, et al. *Neurosci Biobehav Rev.* 2023;151:105209.

Prevalence of Comorbid Disorders in Adults With ADHD

Obesity[1]

Diabetes[2]

Cardiovascular disease[3]

Rheumatoid arthritis[3]

Migraine[3]

1. Cortese S. *Brain Sci.* 2019;9(10):256. 2. Garcia-Argibay M, et al. *Neurosci Biobehav Rev.* 2023;147:105076. 3. Garcia-Argibay M, et al. *Transl Psychiatry.* 2022;12(1):152.

ADHD Impacts Functioning

- Fewer romantic relationships
- Lower marital satisfaction
- Higher rates of divorce

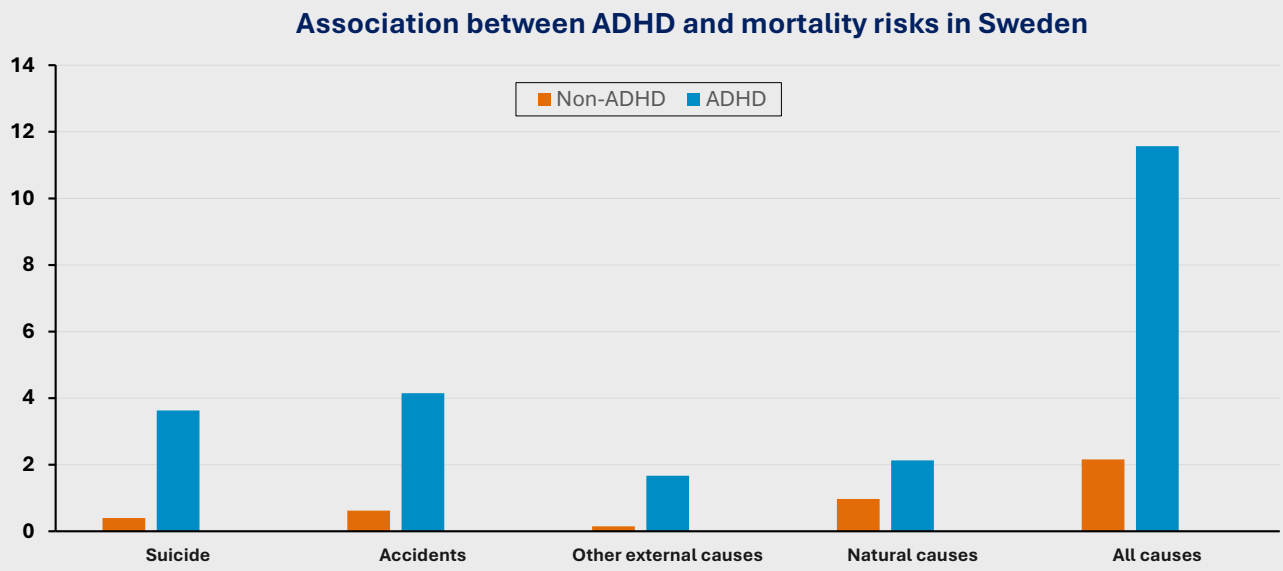
- Poorer social skills
- More friendship problems
- More likely to be lonely

- Less likely to attend college (27% vs 5%)
- Less likely to be employed (<25% vs >70%)

- More likely to have received a speeding ticket (100% vs 56%)
- More likely to have a car crash (80% vs 52%)

Kosheleff AR, et al. *J Atten Disord*. 2023;27(7):669-697.

ADHD and Mortality



Sun S, et al. *JAMA Psychiatry*. 2019;76(11):1141-1149 (including supplemental materials).

How Do You Evaluate ADHD?

Obtain a thorough medical and psychiatric history

- Interview patient/caregiver
  - Core symptoms and associated features
  - Comorbid symptoms
- Consider obtaining collateral information
  - Teacher
  - Significant other

Consider using rating scales

- Useful when screening
- Identify core symptoms
- Identify associated features
- Identify comorbid symptoms
- Are not used to make a diagnosis

ADHD Rating Scales

Children and adolescents

- Vanderbilt Assessment Scale
- ADHD Rating Scale-5
- Conners 4th edition
- Behavior Assessment System for Children (BASC)
- Child Behavior Checklist (CBCL)

Adults

- Adult ADHD Self-Report Scale (ASRS V1.1)
- Brown Attention Deficit Disorder Symptoms Assessment Scale
- Conners Adult ADHD Rating Scales (CAARS)

Children and Adults with Attention-Deficit/Hyperactivity Disorder (CHADD). Which ADHD rating scales should primary care physicians use? 2/9/2017 (https://chadd.org/adhd-weekly/which-adhd-rating-scales-should-primary-care-physicians-use/). Accessed 10/17/2026.

Rating Scales for Comorbid Symptoms

Depression

- Patient Health Questionnaire (PHQ-9)
- Children's Depression Inventory (CDI)

Anxiety

- General Anxiety Disorder Questionnaire (GAD-7)
- Screen for Child Anxiety Related Disorders (SCARED)

Spitzer RL, et al. *JAMA*. 1999;282:1737-1744. Birmaher B, et al. *J Am Acad Child Adolesc Psychiatry*. 1997;36(4):545-553.

ADHD Neurobiology

- Role of dopamine and norepinephrine in ADHD is widely accepted
- Role of serotonin (5HT) is less well characterized
- 5HT receptors and the 5HT transporter regulate 5HT levels
- 5HT neurons innervate nearly every region of the central nervous system
- Evidence supports the role of 5HT in ADHD

Faraone SV, et al. *Expert Opin Ther Targets*. 2025;29(9):637-654.

Evidence for the Role of Serotonin (5HT) in ADHD

- In hyperactive mice 5HT release is reduced
- Dogs with ADHD-like symptoms have lower serum 5HT concentrations than controls
  - Lower 5HT was linked to aggression, activity, impulsivity, fear, attachment, and sensitivity to touch
- Decreased 5HT levels in the prefrontal cortex are linked to hyperactivity and impulsivity
- Impulsive rats showed lower 5HT turnover and deficits in the medial-frontal cortex
- In rats that have had 5HT depleted in the forebrain, amphetamines are less effective in decreasing impulsivity
- Lisdexamfetamine increases 5HT outflow in the rat prefrontal cortex and striatum

Faraone SV, et al. *Exp Opin Ther Targets*. 2025;29:637-654. Raber J, et al. *J Neurochem*. 1997;68:176-186. Gonzalez-Martinez A, et al. *Animals (Basel)*. 2023;13:1037. Adriani W, et al. *Neurosci Biobehav Rev*. 2003;27:639-651. Winstanley CA, et al. *Psychopharmacology*. 2003;170:320-331. Rowley HL, et al. *J Psychopharmacol*. 2014;28:254-269.

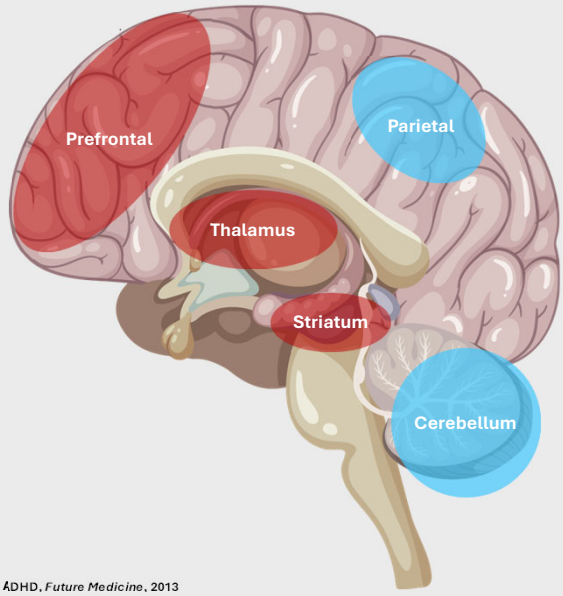
Serotonin in the Brain

Serotonin (5HT) receptors and the 5HT transporter regulate 5HT levels that influence:



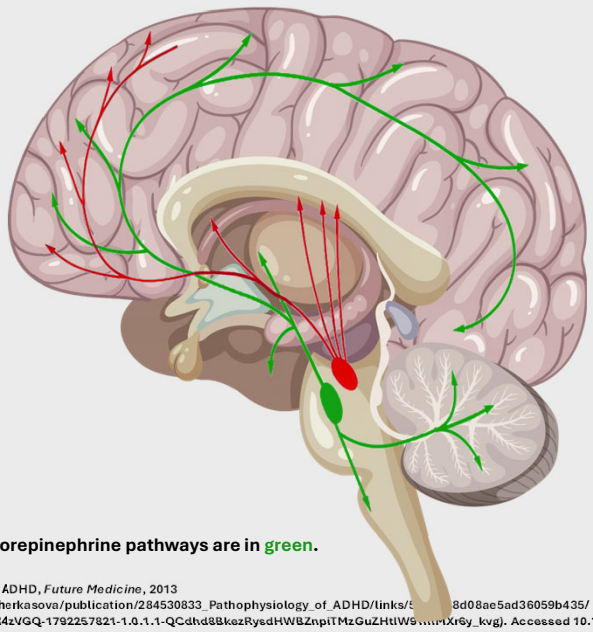
Faraone SV, et al. *Expert Opin Ther Targets*. 2025;29(9):637-654.

Brain Regions Involved in ADHD



Cherkasova M, Hechtman L. Pathophysiology of ADHD, *Future Medicine*, 2013 (https://www.researchgate.net/profile/MariyaCherkasova/publication/284530833_Pathophysiology_of_ADHD/links/56b6548d08ae5ad36059b435/ Pathophysiology-of-ADHD.pdf?__cf_chl_tk=MqUX5dyEkA4wGTdqxA8TTzpvVuT5imu1FqTQkR4zVGQ-1792257821-1.0.1.1-QCdhd8BkezRysdHWBZnpiTMzGuZHtlW9TmMXr6y_kvg). Accessed 10.17.2026.

Brain Structures



Dopamine pathways are in red, norepinephrine pathways are in green.

Cherkasova M, Hechtman L. Pathophysiology of ADHD, *Future Medicine*, 2013 (https://www.researchgate.net/profile/MariyaCherkasova/publication/284530833_Pathophysiology_of_ADHD/links/5[illegible]8d08ae5ad36059b435/ Pathophysiology-of-ADHD.pdf?__cf_chl_tk=MqUX5dyEkA4wGTdqxA8TTzpvVuT5imu1FqTQkR4zVGQ-1792257821-1.0.1.1-QCdhd8BkezRysdHWBZnpiTMzGuZHtlW9[illegible]Xr6y_kvg). Accessed 10.17.2026.

Dopamine and ADHD

Dopamine system

- Cognition
  - Planning
  - Attention
- Initiation of motor response
- Switching
- Reaction to novelty
- Processing reward

Pathways

- Nigrostriatal
  - Motor control
- Mesolimbic
  - Motivation
  - Reinforcement learning

Dopamine metabolism is flawed in

- Putamen
- Amygdala
- Dorsal midbrain

Del Campo N, et al. *Biol Psychiatry*. 2011;69:e145-157. Khoury NM, et al. *Child Adolesc Psychiatry Clin N Am*. 2022;31:343-361.

Noradrenergic System and ADHD

Norepinephrine

- Neurons originate in locus coeruleus
- Project to prefrontal cortices
- Subcortical structures

Noradrenergic signaling

- Mediates arousal
- Mediates cognition

As a postsynaptic α-2A agonist

- Working memory
- Regulating attention
- Inhibiting behavior
- Planning

Del Campo N, et al. *Biol Psychiatry*. 2011;69:e145-157. Khoury NM, et al. *Child Adolesc Psychiatry Clin N Am*. 2022;31:343-361.

Serotonin

Affects ADHD behaviors in many areas of the brain

- Dorsal raphe nucleus
  - Major source of serotonin neurons
  - Neurons project to prefrontal cortex, amyglada, and basal ganglia
  - Serotonin modulates cognition and behaviors in multiple areas below

Prefrontal cortex	Substantia nigra	Ventral tegmental area	Nucleus accumbens	Hippocampus
• Modulates cognition • Mood regulation • Impulse control	• Modulates dopamine release and reuptake • Influences motor function	• Modulates activity of dopamine neurons	• Reward circuitry • In depression and addiction	• Modulates learning • Memory • Emotions

Faraone SV, et al. *Expert Opin Ther Targets*. 2025;29(9):637-654.

Multiple Brain Regions and Networks Are Involved in ADHD

Executive control network
Planning, goal-directed behavior, attention, inhibition, working memory, timing, and cognitive flexibility

Frontoparietal network
Coordinates behavior in rapid, accurate, and goal-directed way

Default mode network
Active at rest
Self-reflection, emotional processing, social interactions, and mental exploration

Reward network
Activated with rewarding stimuli and dopamine is released

Faraone SV, et al. *Nat Rev Dis Primers*. 2024;22;10:11. Azarias F, et al. *Biology (Basel)*. 2025;14:395. Marek S, et al. *Dialogues Clin Neurosci*. 2018;20:133-140. Lewis RG, et al. *Adv Exp Med Biol*. 2021;1344:57-69.

Currently Marketed ADHD Medications

Stimulants

- Amphetamine
- Methylphenidate
- Centanafadine

Nonstimulants

- Atomoxetine
- Viloxazine ER
- Clonidine ER
- Guanfacine ER

ER = extended-release.

Stimulants

Amphetamine

Increases extracellular dopamine (DA) and norepinephrine (NE)

- DA and NE transporter inhibition
- Increasing vesicular DA release
  - Vesicular monoamine transporter 2 (VMAT-2) inhibition
- Monoamine oxidase activity inhibition
  - Decreases breakdown of monoamines in the neuron

Methylphenidate

Increases extracellular DA and NE levels

- DA and NE transporter inhibition
- Agonist activity at the serotonin type 1A receptor
- Redistribution of VMAT-2

Faraone S. *Neurosci Biobehav Rev*. 2018;87:255-270.

Stimulant: Centanafadine

Norepinephrine, dopamine, and serotonin reuptake inhibitor

Central nervous system stimulant

Drug-drug interactions

- No meaningful change in CYP1A2 inhibitors/inducers and CP2D6 inhibitors
- Caffeine area under the curve doubles when administered with centanafadine

Centanafadine ER (Simtriyo®) PI 2026 (https://www.accessdata.fda.gov/drugsatfda_docs/label/2026/218145s000lbl.pdf). Accessed 10/17/2026.

Nonstimulants

Atomoxetine

- Norepinephrine reuptake inhibitor
- Increases DA levels in the prefrontal cortex
- Does not increase DA in striatum or nucleus accumbens
- Weak effects at serotonin transporter

Guanfacine ER

- Selective NE α2A-adrenocepter agonist
- Improves prefrontal cortex cognitive functions

Clonidine ER

- Stimulates α2 adrenergic receptors in the brain

Bymaster F, et al. *Neuropsychopharmacology.* 2002;27:699-711. Arnsten AFT. *Neurobiol Learn Mem.* 2020;176:107327. Clonidine hydrochloride (Kapvay®) Prescribing information (PI) 2020 (https://www.accessdata.fda.gov/ drugsatfda_docs/label/2020/022331s021lbl.pdf). Accessed 10/17/2026.

Adverse Events (AEs) Associated With Current Treatments

95% of participants reported at least 1 AE

Average number of AEs was 5.8

73.2% reported skipping doses

19.9% of those skipped due to AE

AAQOL* average 46.4

(non-ADHD average is ~79)

*AAQOL = Adult Attention-Deficit/Hyperactivity Disorder Quality of Life Scale.

Schein J, et al. *Curr Med Res Opin*. 2023;39(1):149-159.

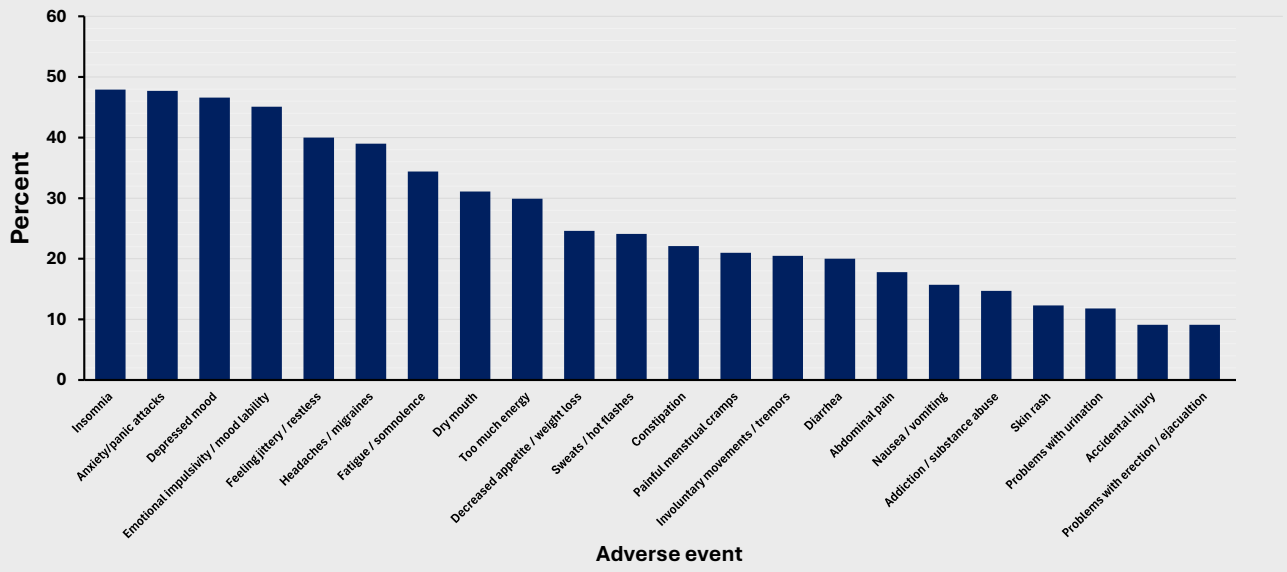
Reasons for Treatment Switch or Discontinuation

In a chart-review study of 320 patients

- Most common reasons for discontinuation were
  - Suboptimal symptom management: 55.9%
  - ADHD/treatment related complications: 25.4%
  - Patient attitude/dislike of medication: 25.4%
- Most common adverse events leading to discontinuation were
  - Anxiety/panic attacks
  - Hypertension
- More than 40% of patients switched treatments at least 1 time

Schein J, et al. *BMC Psychiatry*. 2022;22:377.

ADHD Adverse Events With Treatment



Schein J, et al. *Curr Med Res Opin*. 2023;39(1):149-159.

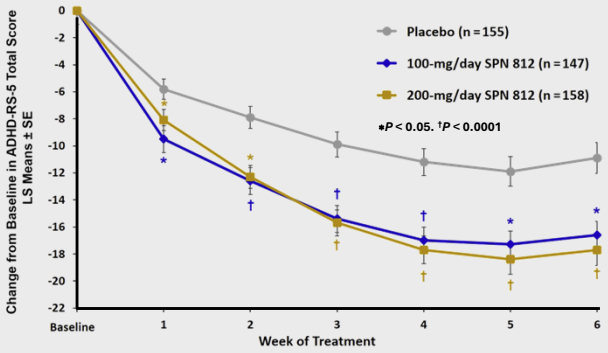
Viloxazine Extended-Release (ER)

- Pharmacology[1,2]
- Norepinephrine reuptake inhibitor
- Serotonin receptor partial agonist (5-HT2C) and antagonist (5-HT2B)
- Immediate-release formulation was marketed as antidepressant in Europe
- Metabolism[1,3]
  - CYP1A2: Increases exposure to caffeine and melatonin
  - CYP2D6, CYP3A4: Weak inhibitor
  - Primarily metabolized by CYP2D6, UGT1A9, and UGT2B15

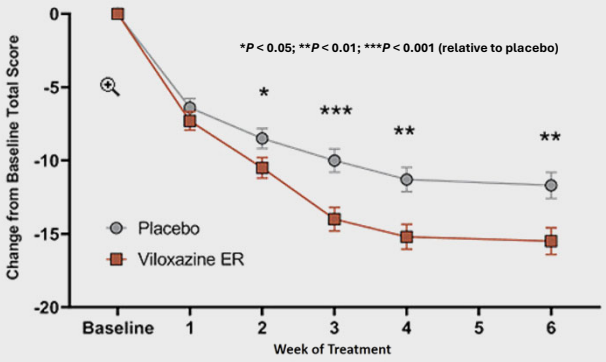
1. Yu C. *Xenobiotica*. 2020;50:1285-1300. 2. Yu C, et al. *J Exp Pharmacol*. 2020;12:285-300. 3. *New drug application (NDA) 211964 Viloxazine ER integrated review*, 4/2/2021.

Efficacy of Viloxazine ER in ADHD

Efficacy in children with ADHD

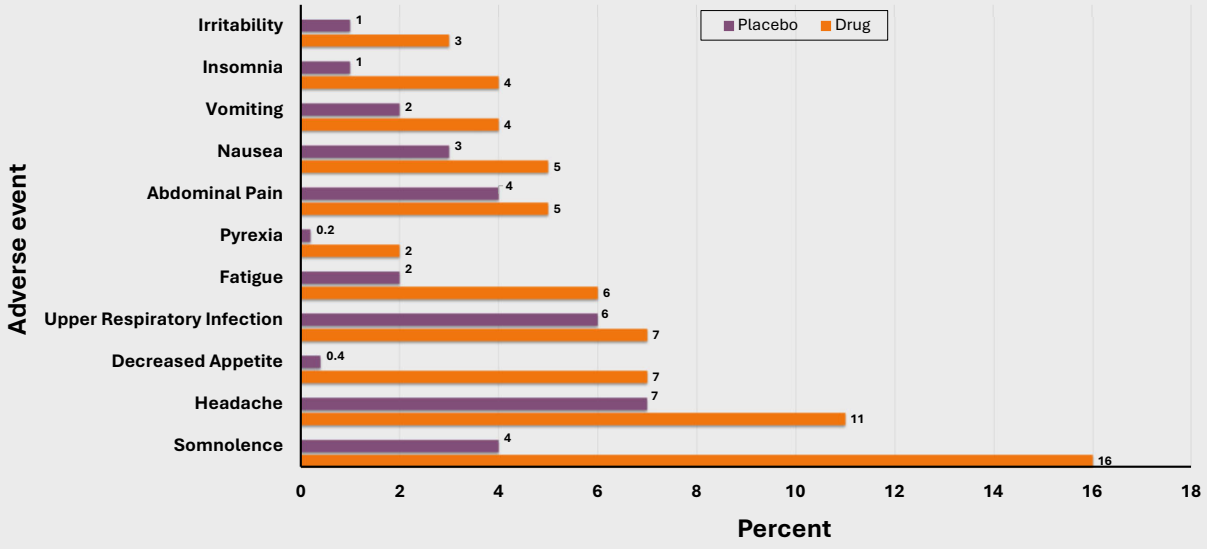


Efficacy in adults with ADHD



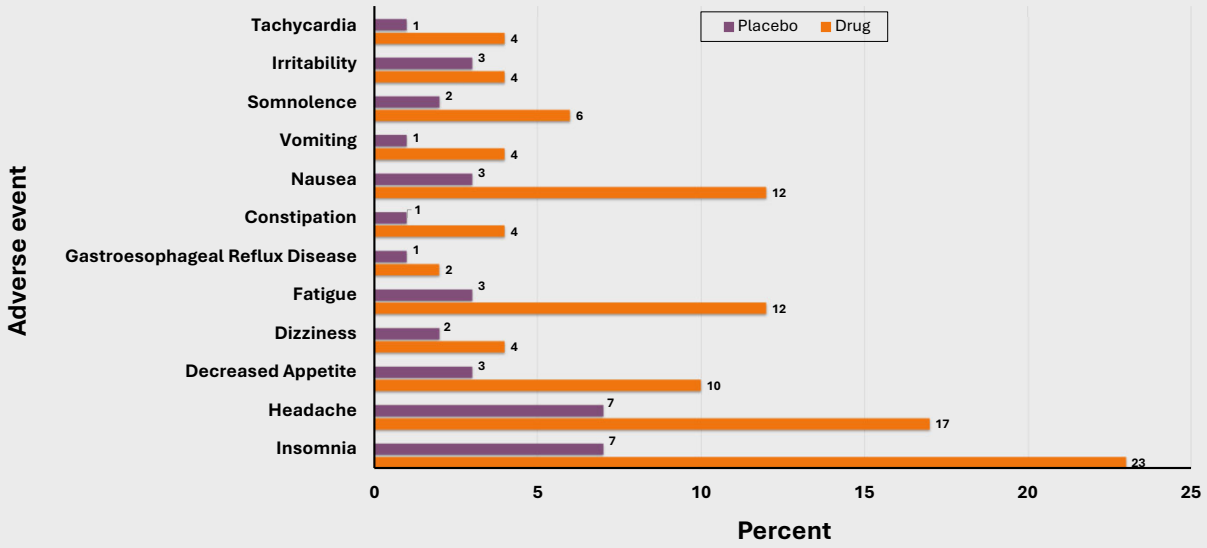
Nasser A, et al. *Clin Ther*. 2020;42:1452-1466. Nasser A, et al. *CNS Drugs*. 2022;36(8):897-915.

Viloxazine ER Adverse Effects in Patients 6 to 17 Years ≥2% and > Placebo



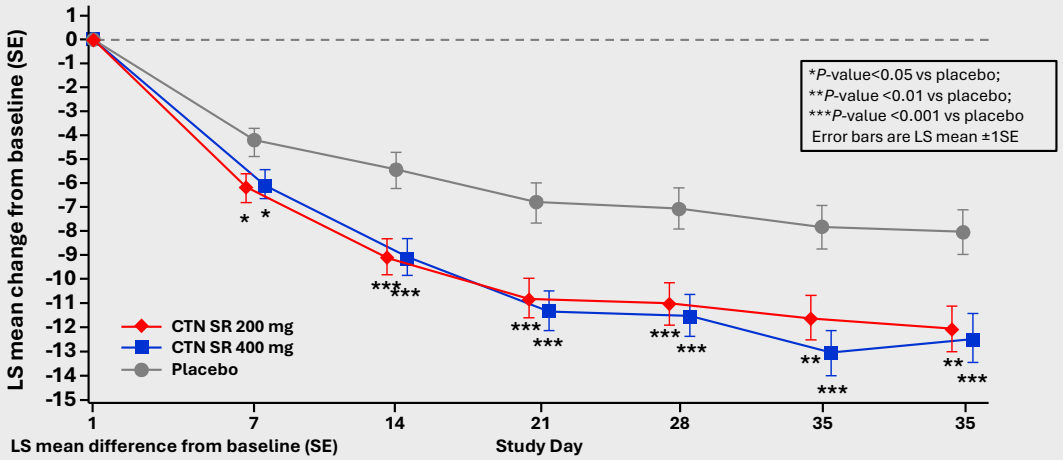
Nasser A, et al. *Clin Ther*. 2020;42:1452-1466. Nasser A, et al. *CNS Drugs*. 2022;36(8):897-915. Viloxazine ER (Qelbree®) PI 2025 (https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/211964s013lbl.pdf). Accessed 10/17/2026.

Viloxazine ER Adverse Effects in Adults ≥2% and > Placebo



Viloxazine ER (Qelbree®) PI 2025 (https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/211964s013lbl.pdf). Accessed 10/17/2026.

Centanafadine: AISRS† Total Score Change

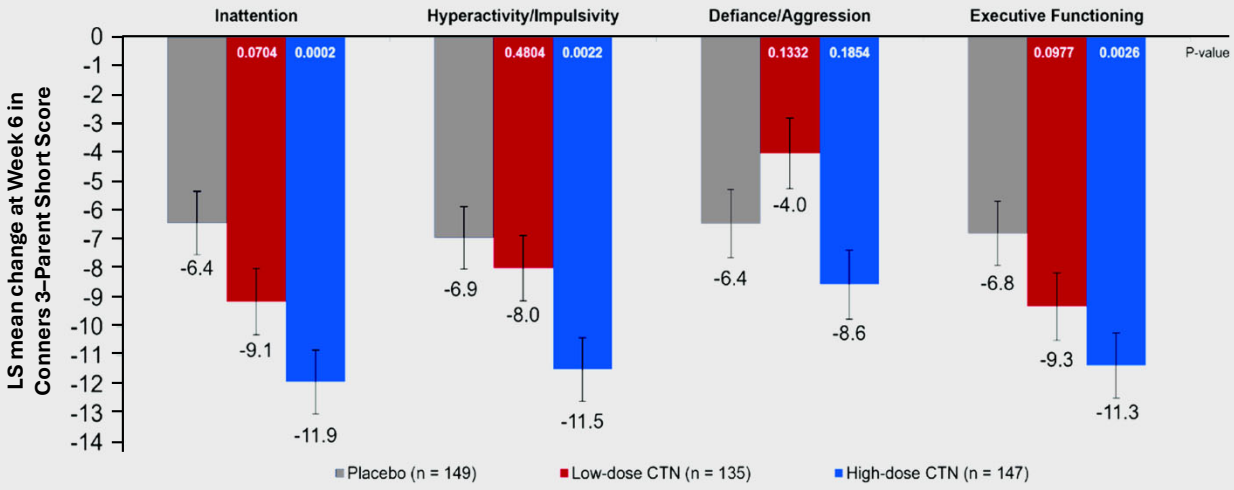


LS mean difference from baseline (SE)						
CTN SR 200 mg	–6.21 (0.62)	–9.09 (0.78)	–10.83 (0.82)	–11.02 (0.86)	–11.61 (0.91)	–12.08 (0.96)
CTN SR 400 mg	–6.09 (0.62)	–9.09 (0.78)	–11.31 (0.84)	–11.56 (0.89)	–13.09 (0.93)	–12.49 (0.99)
Placebo	–4.28 (6.01)	–5.44 (0.76)	–6.81 (0.81)	–7.08 (0.85)	–7.84 (0.89)	–8.07 (0.94)

†AISRS = Adult ADHD Investigator Symptom Rating Scale.
LS = least-squares; SE = standard error.

Adler LA, et al. *J Clin Psychopharmacol*. 2022;42(5):429-439.

Centanafadine: Conners Change From Baseline in Children



Ward CL, et al. *Pediatrics Open Sci.* 2025;1(3):1-11.

Centanafadine Adverse Events

Adverse event	Children	Adolescents	Adults
Rash	9%	8%	4%
Decreased appetite	8%	15%	7%
Fatigue	4%	3%	
Abdominal pain	4%	5%	4%
Nausea	3%	10%	7%
Pharyngitis streptococcal	3%		
Diarrhea	2%		5%
Influenza	2%		
Somnolence		4%	
Headache		7%	8%
Dizziness		3%	

Centanafadine ER (Simtriyo®) PI 2026 (https://www.accessdata.fda.gov/drugsatfda_docs/label/2026/218145s000lbl.pdf). Accessed 10/17/2026.

Centanafadine Adverse Events (cont)

Adverse event	Children	Adolescents	Adults
Nasopharyngitis		3%	
Insomnia		3%	7%
Irritability		3%	4%
Dry Mouth		2%	6%
Weight Decreased		2%	
Parasomnia			3%
Tachycardia			2%
Depressed mood			2%
Anxiety			2%
Upper respiratory infection			2%

Centanafadine ER (Simtriyo®) PI 2026 (https://www.accessdata.fda.gov/drugsatfda_docs/label/2026/218145s000lbl.pdf). Accessed 10/17/2026.

Review of Learning Objectives

- Implement comprehensive evaluation techniques to identify the broader clinical features of ADHD and factors that influence functional impairment and disease burden
- Identify the neurobiological underpinnings of ADHD including the role of and interplay between dopamine, norepinephrine, and serotonin
- Apply clinical evidence for current and emerging ADHD pharmacotherapies, including their strengths and limitations, to inform treatment selection and comprehensive disease management of ADHD

Thank you!

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