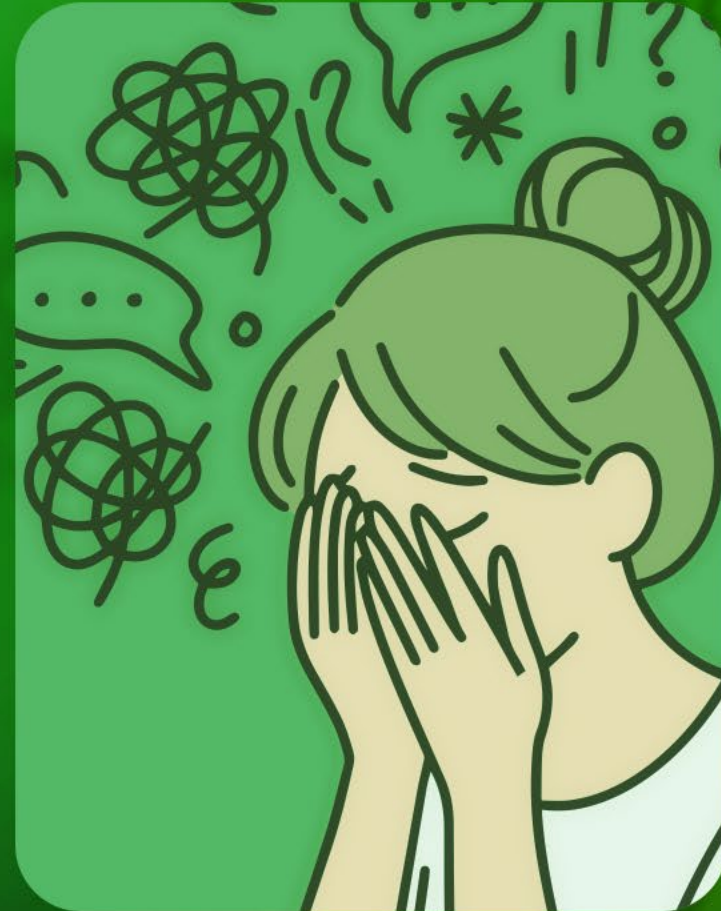


Features Out of Focus:
***Recognition and
Treatment of Emotional
Dysregulation and
Executive Dysfunction
in ADHD***

Module 4



Faculty

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Faculty Disclosures

- **Greg Mattingly, MD:** Consultant – AbbVie, Acadia, Akilli, Alkermes, Angelini, Axsome, Aytu, Biogen, BMS, Boehringer Ingelheim, Cerevel, Corium, Eisai, GH Research, Intracellular, Ironshore, Johnson & Johnson, Liva Nova, Lumos Labs, Lundbeck, Neurocrine, Noven, Otsuka, Redax, Relmada, Revibe, Roche, Sage, Sirona, Sky Therapeutics, Sunovion, Supernus, Takeda, Teva, Tris Pharma; Research – AbbVie, Acadia, Aytu, Alkermes, Akilli, Alto Therapeutics, Avanir, Axsome, BMS, Boehringer Ingelheim, Cingulate, Click Therapeutics, Croium, Emalex, Idorsia, Intracellular, Johnson & Johnson, Karuna, Lumos Labs, Medgenics, Neurocrine, NLS Pharma, Redax, Relmada, Roche, Sage, Sirtsei, Sumitomo, Sunovion, Supernus, Takeda, Teva, Transcend; Speakers Bureau – AbbVie, Alkermes, Angelini, Axsome, BMS, Corium, Intracellular, Ironshore, Johnson & Johnson, Lundbeck, Neurocrine, Noven, Otsuka, Sunovion, Supernus, Takeda, Teva, Tris Pharma

Disclosures

- The faculty have been informed of their responsibility to disclose to the audience if they will be discussing off-label or investigational use(s) of drugs, products, and/or devices (any use not approved by the US Food and Drug Administration)
- Applicable CME staff have no relationships to disclose relating to the subject matter of this activity
- This activity has been independently reviewed for balance
- This CME activity includes brand names for participant clarity purposes only. No product promotion or recommendation should be inferred

Learning Objectives

- Assess the pharmacologic and clinical safety and efficacy profiles of conventional, novel, and investigational agents for ADHD, including consideration of their potential to address often under-addressed symptoms/features of the disorder

Evaluation of Current and Emerging Pharmacotherapies to Address Unmet Needs

Strengths and Limitations of Traditional Stimulant Pharmacotherapies

Some Strengths of Traditional Stimulants	Some Limitations of Traditional Stimulants
High efficacy in reducing core ADHD symptoms in children and adults (70-80% response rates)	Common adverse effects: appetite suppression, insomnia, irritability, headache, anxiety, dizziness, nausea
Rapid onset of action with noticeable improvement within hours to days	Growth concerns in youth due to appetite/weight suppression
Strong evidence base with decades of clinical research and guideline support	Increased cardiovascular risk; increased heart rate and blood pressure; requires monitoring
Multiple formulations (IR, ER, prodrug) allow individualized treatment; long-acting options improve adherence and convenience	Risk of misuse/diversion, especially in adolescents and adults
Improves academic, occupational, executive, and social functioning	Schedule II classification creates prescribing and refill restrictions; potential shortages
Well-established dosing/titration strategies familiar to clinicians	May cause or worsen sleep disturbances, aggression, irritability, hostility, anxiety, mood swings

Current Landscape of ADHD Medications*:

Traditional Stimulants, Nonstimulants, & Novel Stimulants

FDA-Approved for ADHD

Traditional stimulants: methylphenidate, dexamethylphenidate, serdexmethylphenidate/dexamethylphenidate, dextroamphetamine, lisdexamfetamine, amphetamine/mixed amphetamine salts

Nonstimulants: atomoxetine, viloxazine ER, clonidine XR, guanfacine XR

Novel stimulants: centanafadine

Not FDA-Approved for ADHD

Off-label agents: TCAs, bupropion, modafinil/armodafinil

In Phase 3 development: solriamfetol



Development status:

- Adult Phase 3 FOCUS trial met its primary endpoint
- Adolescent Phase 3 FOCUS-3 trial ongoing

*Approved ages and indications vary by agent and formulation.

TCA = tricyclic antidepressants.

US Food and Drug Administration. Treating and Dealing With ADHD. Updated May 30, 2023; Cortese S, et al. Lancet Psychiatry. 2018;5(9):727-738; ClinicalTrials.gov. NCT05972044.

Nonstimulants Overview

Atomoxetine

MOA: norepinephrine reuptake inhibitor (NRI)

Showed significant improvement in ADHD symptoms in 4 studies in children/adolescents and 2 studies in adults

Studies have also shown efficacy for function QoL, executive function, oppositionality, emotional lability, and anxiety, but NOT for depression

Clonidine XR & Guanfacine XR (alpha-2 agonists)

MOA: agonism of noradrenergic alpha 2A (presynaptic) and 2C (postsynaptic) receptors

Both approved (XR only) as monotherapy or adjunct to stimulants, but only for ages 6-17.

Both also used for ODD and emotional dysregulation.

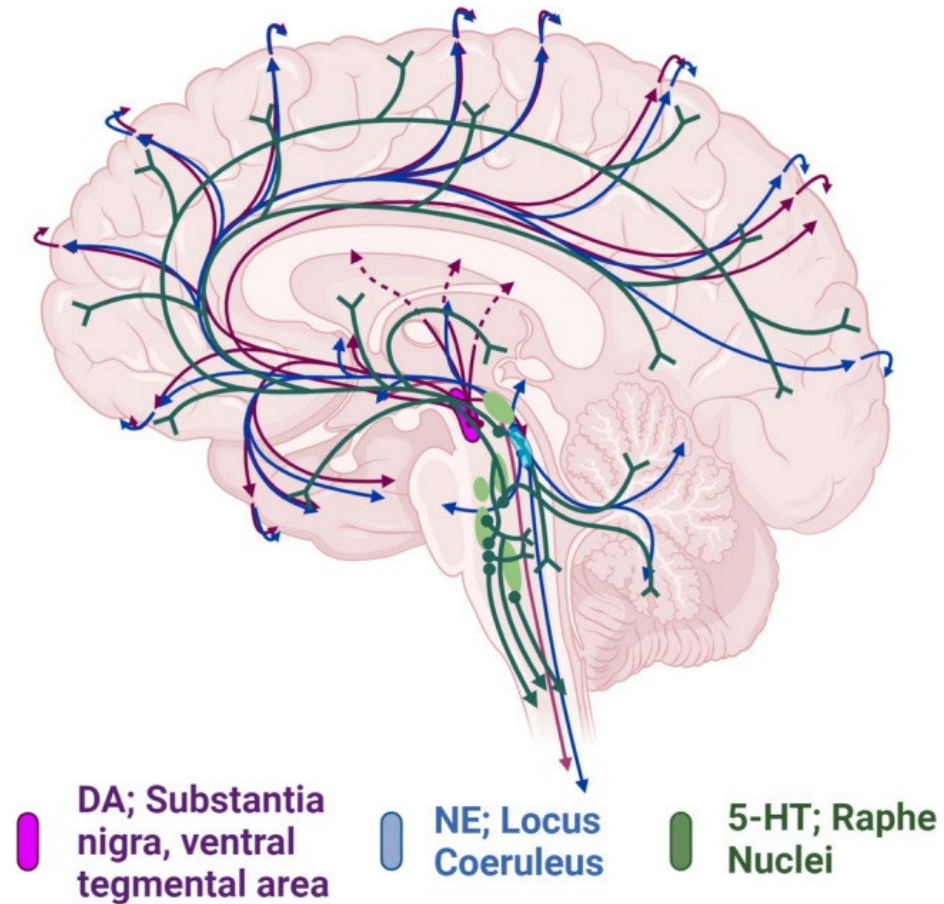
Clonidine XR is now available as tablet (BID) or liquid (QHS)

Guanfacine XR “selective” for alpha 2A?

...But What About Serotonin?

Serotonin signaling is closely tied to dopamine and norepinephrine

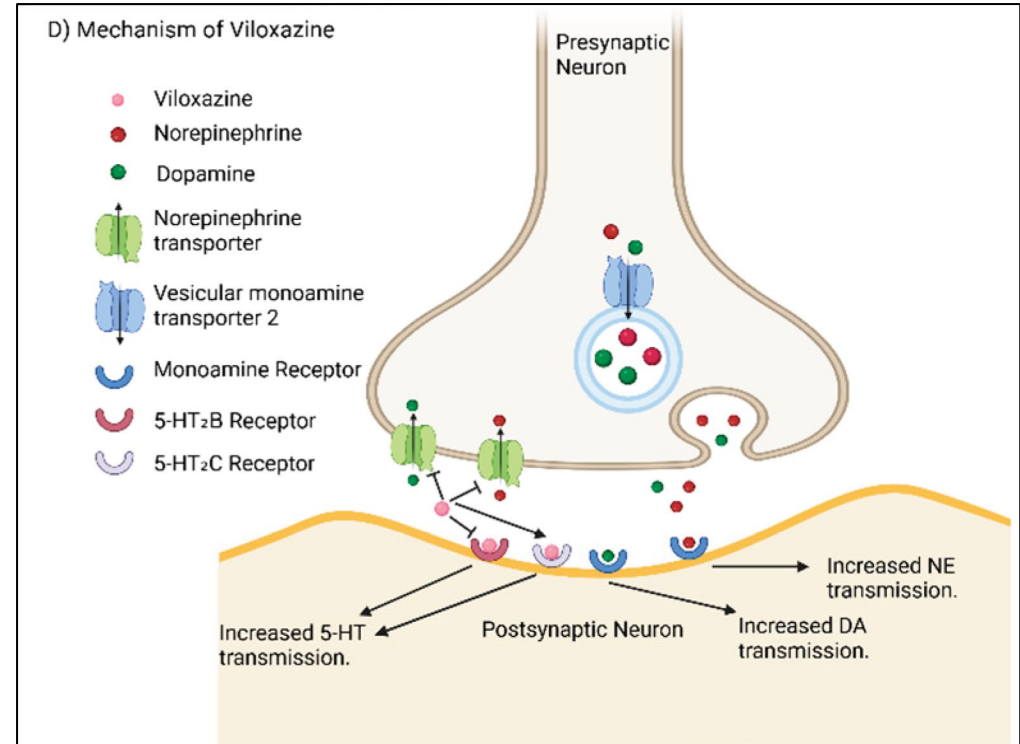
How can we target this system pharmacologically?



Viloxazine ER

Viloxazine ER

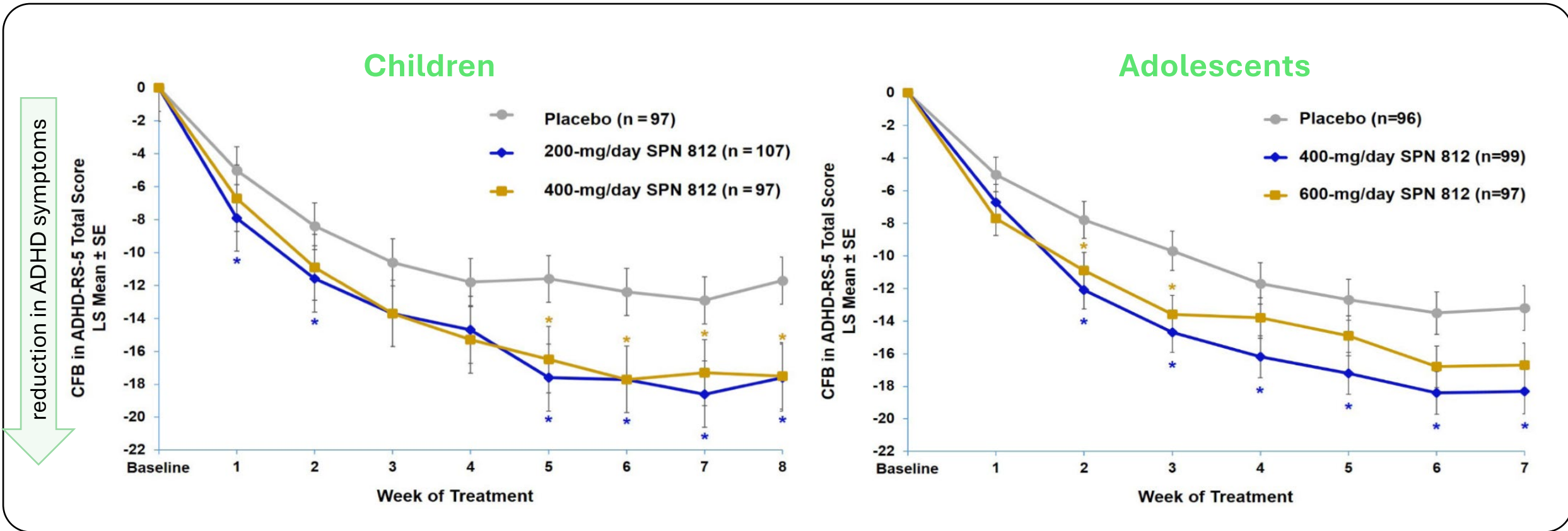
- **MOA:** NRI, 5HT_{2C} partial agonist, and 5HT_{2B} & 5HT₇ antagonist
 - IR formulation approved for MDD in the EU, but never in the US
- FDA approved for children, adolescents, and adults



MOA=mechanism of action

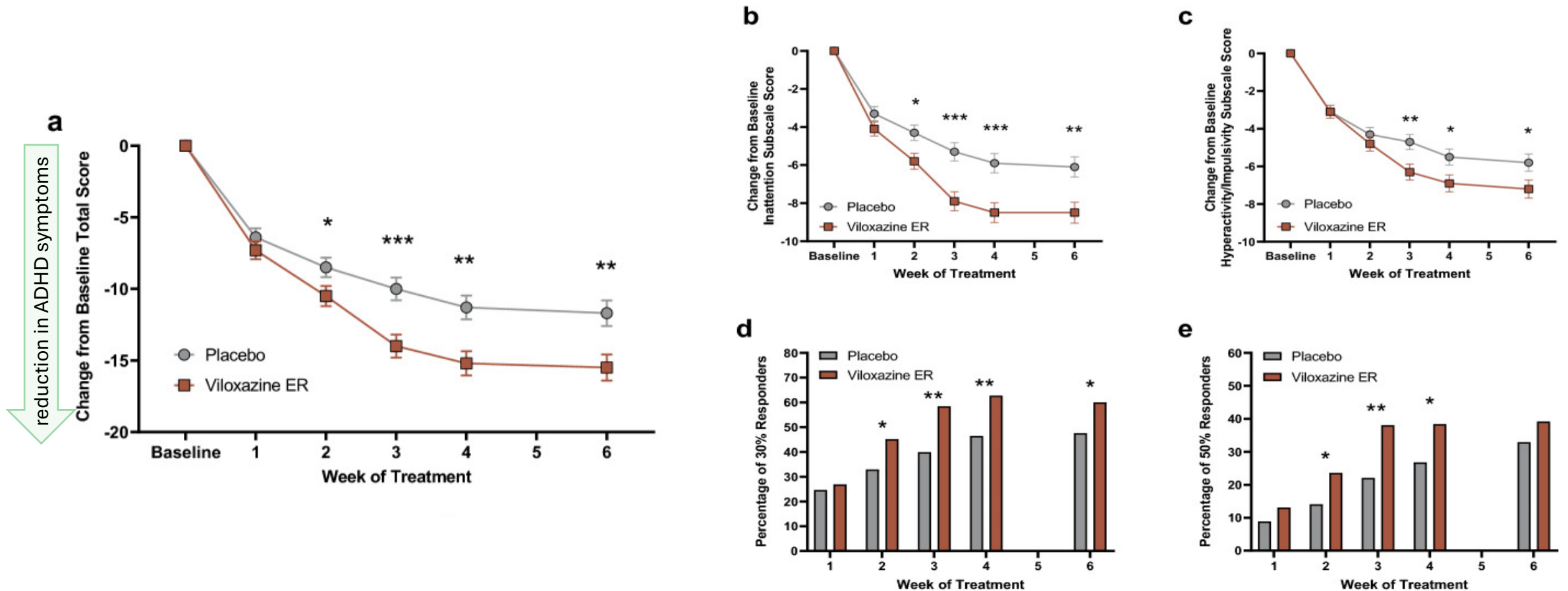
Edinoff AM, et al. Front Psychiatry. 2021 Dec 17;12:789982. Nasser A, et al. CNS Drugs. 2022 Jul;36(8):897-915. Childress AC, et al. J Child Adolesc Psychopharmacol. 2025 Apr;35(3):155-166. Yacoub MW, et al. Cells. 2025;14(17):1367

Viloxazine ER Efficacy: Children & Adolescents



Across pediatric and adolescent trials, viloxazine ER (SPN-812) demonstrated significant and sustained reductions in ADHD symptoms over 6–8 weeks compared to placebo.

Viloxazine ER for Adult ADHD



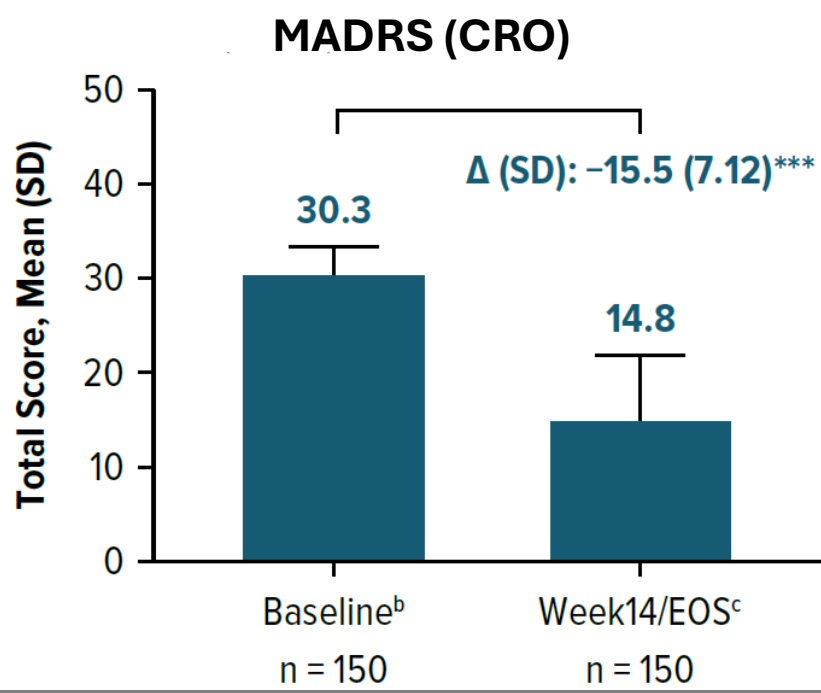
In an adult trial, **viloxazine ER significantly reduced overall ADHD symptoms**, including inattention and hyperactivity/impulsivity, over 6 weeks of treatment compared to placebo.

Viloxazine ER for Adults with ADHD and Comorbid Mood and Anxiety Symptoms

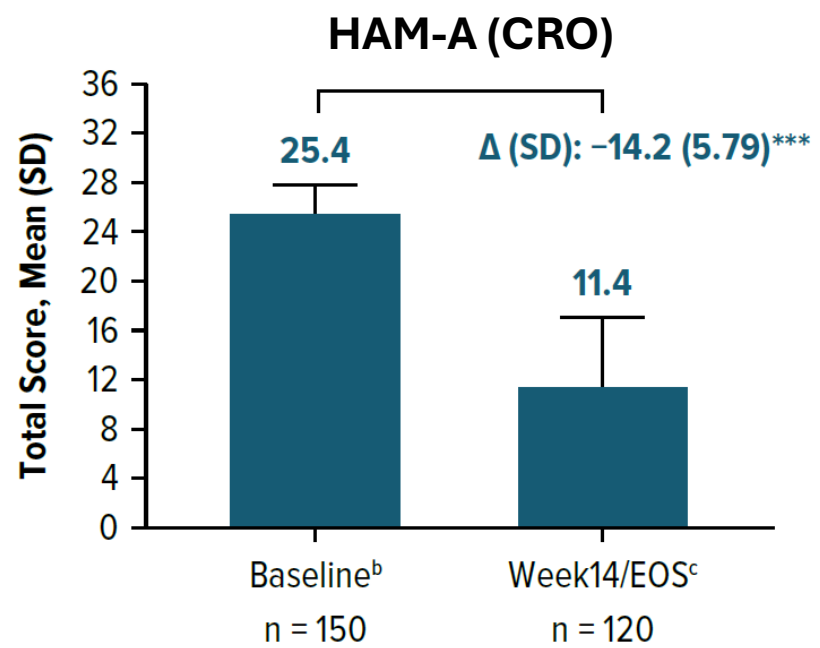
All clinician and patient reported outcomes were significant and showed > 50% improvement

Safety population, N=161	
Age (years), mean ± SD	39.5 ± 10.6
Sex, female	75.2%
Race, white	79.5%
BMI (kg/m²), mean ± SD	31.7 ± 9.0
College degree (2 or 4 year)	36.0%
Currently employed	72.1%
Married	37.9%
Total AISRS, mean ± SD	37.4 ± 6.5
Total MADRS, mean ± SD	30.3 ± 3.1
Total HAM-A, mean ± SD	25.4 ± 2.3
Total MADRS >22	100%
Total HAM-A >22	99.4%
Total MADRS >22 and HAM-A >22	99.4%

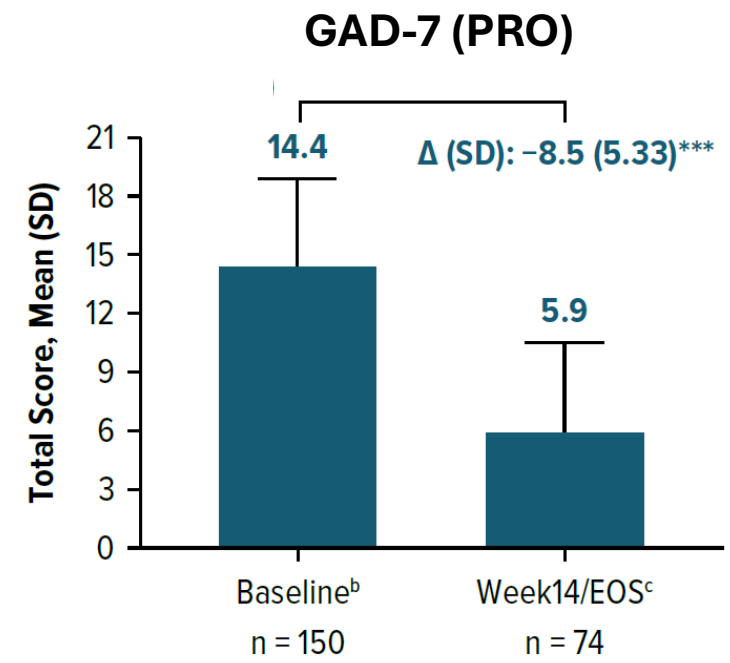
Viloxazine ER Improved Depressive and Anxiety Symptoms in Adults with ADHD in Open-Label Ph4 Trial



Clinician-rated depressive symptom scores showed ~49% improvement from baseline to Week 14



Clinician- and patient-rated anxiety symptom scores showed >50% improvement from baseline to Week 14



CRO = clinician-rated outcome; PRO = patient-rated outcome.
Adler LA, et al. J Clin Psychiatry. 2026;87(2):25m16234.

Viloxazine ER Safety and Tolerability



Across age groups, viloxazine ER was **generally safe** and **well-tolerated**



In children (6-11yo), **55.1%** of participants treated with SPN-812 experienced an AE

- Most common: somnolence, decreased appetite, fatigue, headache, and upper abdominal pain



In adolescents (12-17yo), **56.8%** of participants treated with SPN-812 experience an AE

- Most common: somnolence, fatigue, headache, nausea, and decreased appetite



In adults (18-65yo), **60.3%** of participants randomized to viloxazine ER experienced a TEAE

- Most common: insomnia, fatigue, nausea, decreased appetite, dry mouth, and headache

AE=adverse event; TEAE=treatment-emergent adverse event

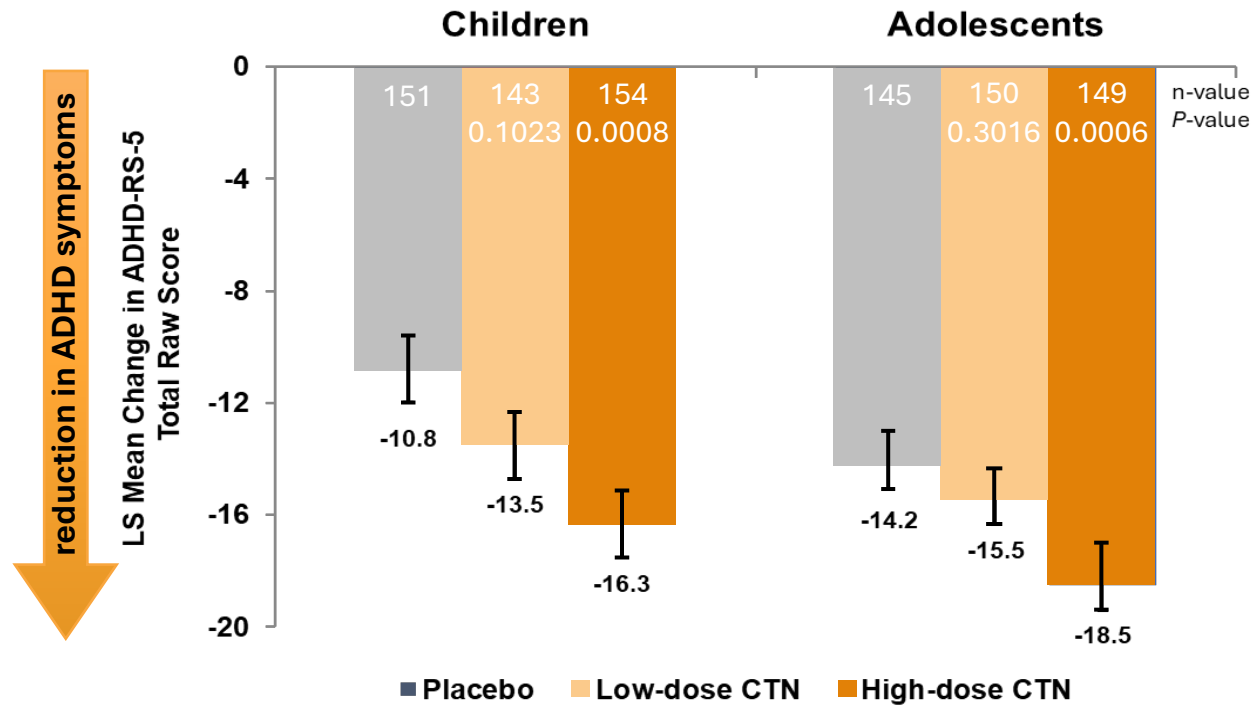
Nasser A, et al. Clin Ther. 2021;43(4):684-700; Nasser A, et al. Psychopharmacol Bull. 2021;51(2):43-64; Nasser A, et al. CNS Drugs. 2022 Jul 27;36(8):897-915.

Centanafadine

Centanafadine ER in Children and Adolescents

Children: mean change from baseline in ADHD-RS-5 at Week 6 was -16.3 for high-dose CTN versus -10.8 for placebo ($P=0.0008$), with benefit seen as early as Week 1 ($P=0.0009$)

Adolescents: mean change from baseline in ADHD-RS-5 at Week 6 was -18.5 for high-dose CTN versus -14.2 for placebo ($P=0.0006$), with benefit seen as early as Week 1 ($P=0.001$)



Children (weight-based dosing)

Low Dose: 41.1mg, 82.2 mg, 123.3mg, 164.4mg

High Dose: 82.2mg, 164.4mg, 246.6mg, 328.8mg

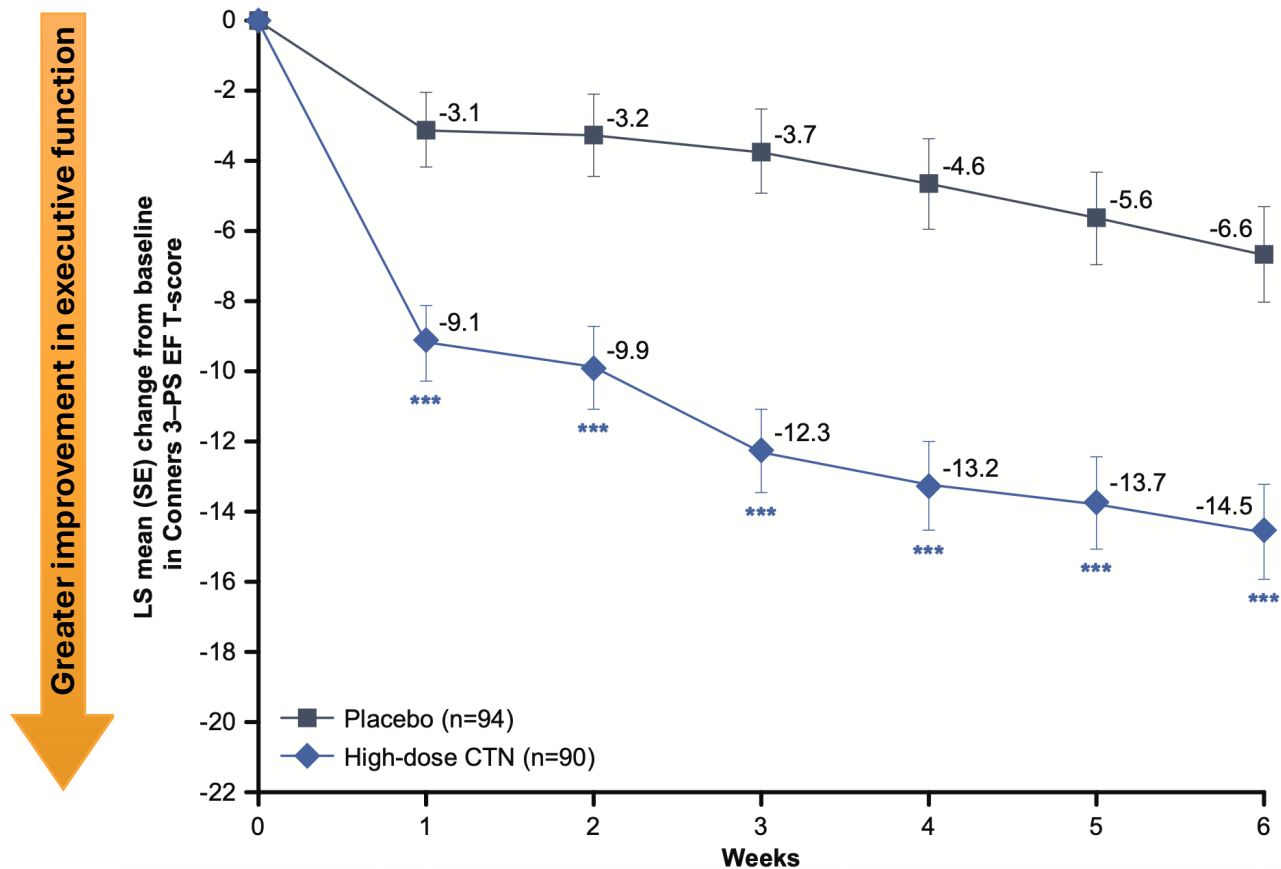
Adolescents

Low Dose: 164.4mg

High Dose: 328.8mg

High-Dose Centanafadine Improved Executive Function in Children and Adolescents with High Baseline Emotional Dysregulation

A post-hoc analysis of data pooled from two phase 3 clinical trials in children (6-12yo) and adolescents (13-17yo) with **ADHD** and **high baseline emotional dysregulation**[†]



For participants with high baseline emotional dysregulation[†]:

High-dose CTN produced significantly **greater improvements in parent-rated executive function** compared with placebo at all time points over 6 weeks

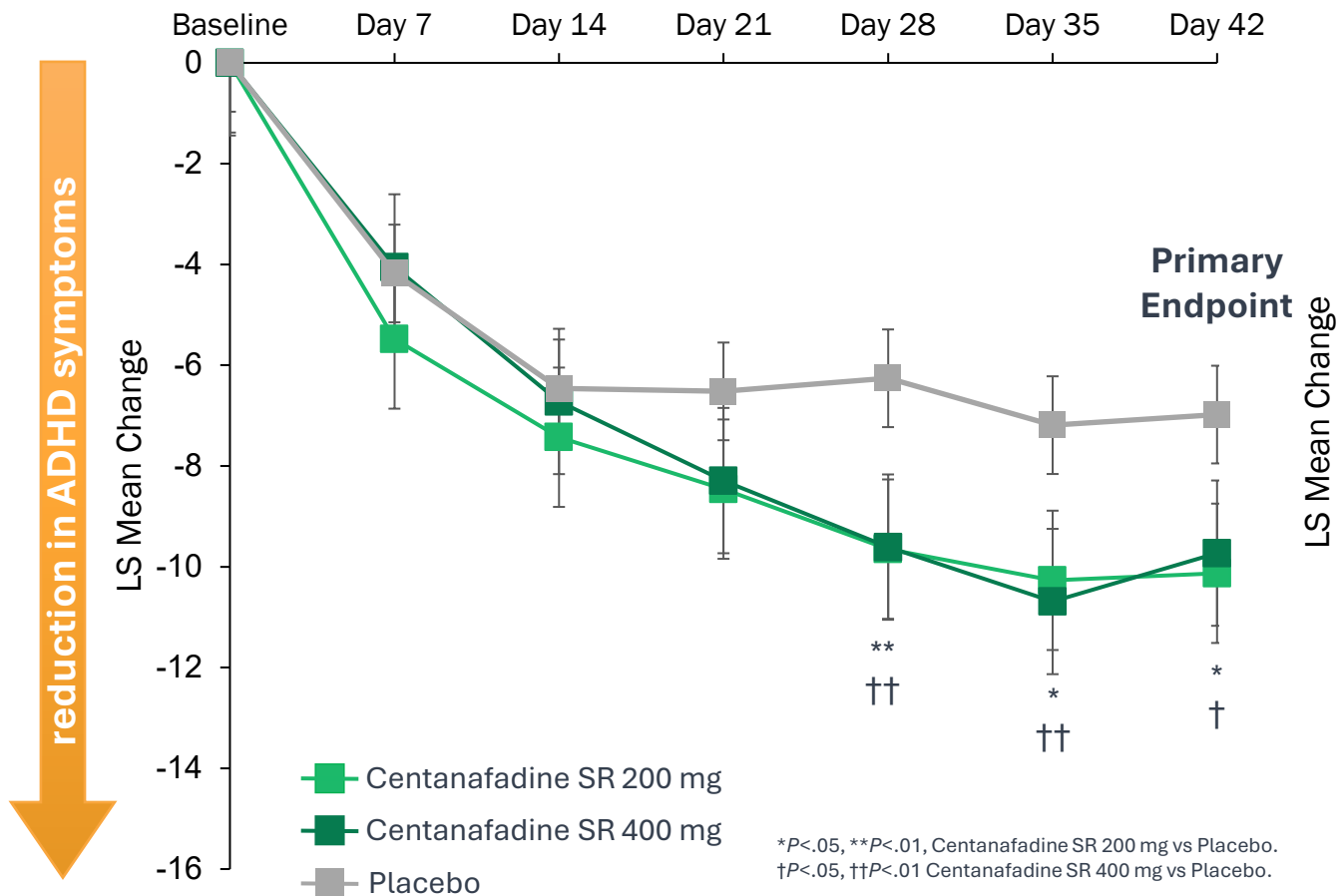
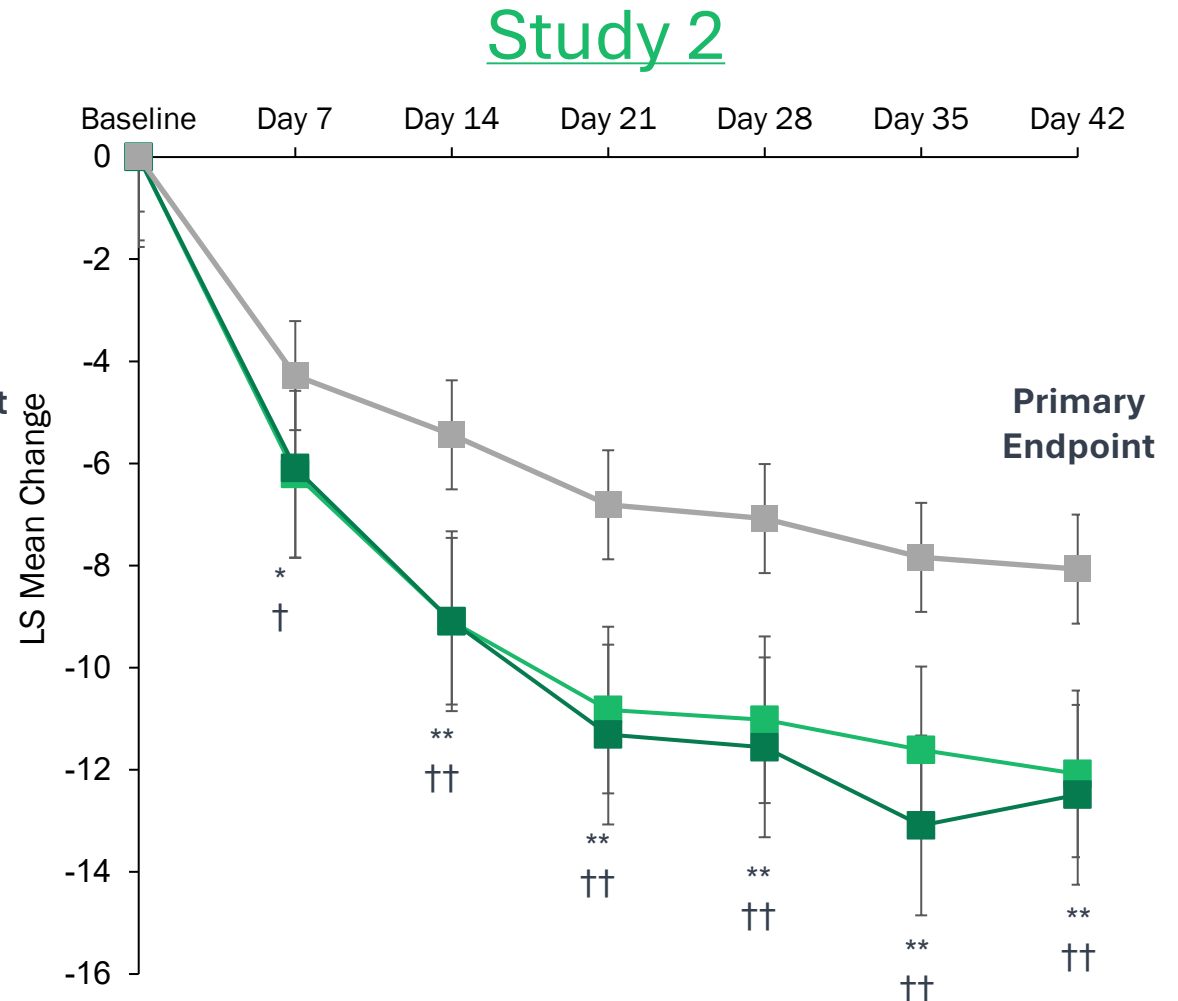
[†] High baseline emotional dysregulation was defined by a baseline Conners 3-PS Defiance/Aggression content scale T-score of ≥ 70 .
***P<0.001

CTN = centanafadine; Conners 3-PS = Conners 3rd Edition-Parent Short; EF = Executive Function.

Ward CL, et al. Efficacy of centanafadine in children and adolescents with ADHD and high baseline emotional dysregulation: post hoc analysis of two phase 3 trials. Poster presented at: American Professional Society of ADHD and Related Disorders (APSARD) Annual Meeting; January 15–18, 2026; San Diego, CA.

Centanafadine SR (200 and 400mg) Improved ADHD Symptoms in Adults in Two Ph3 Trials

Study 1



AISRS=ADHD Investigator Symptom Rating Scale; LS=least squares; MMRM=Mixed Models for Repeated Measures; SR=sustained release.

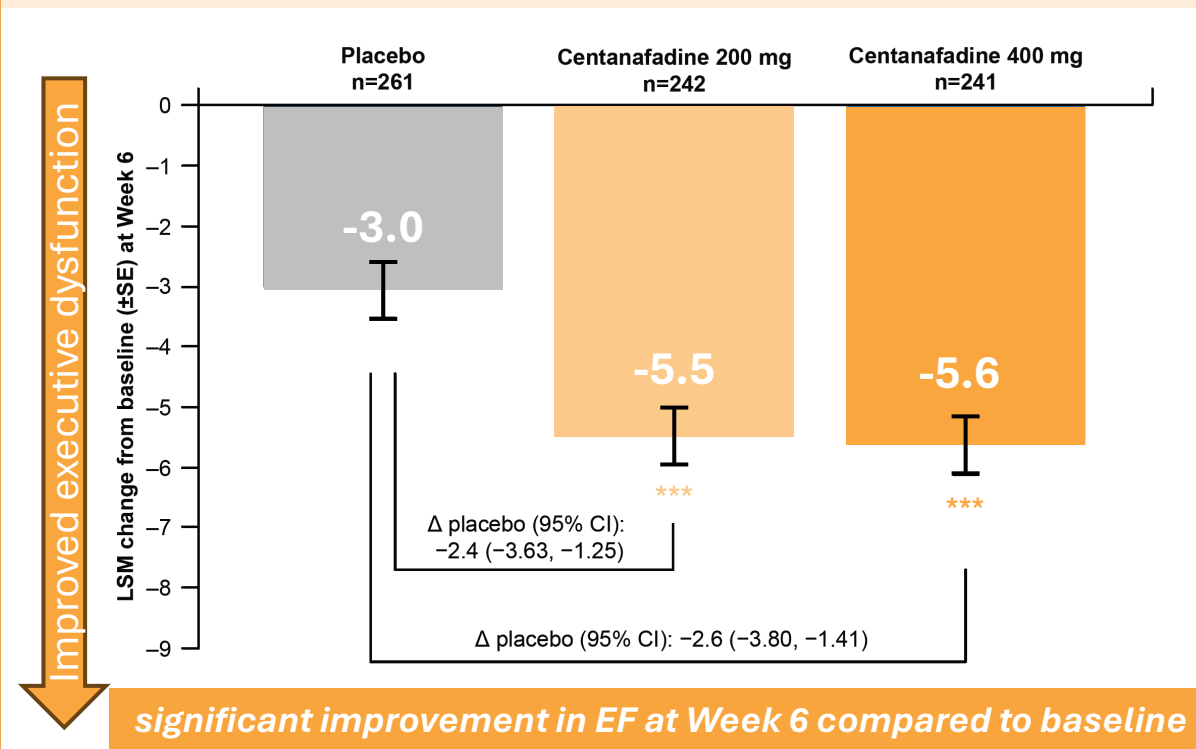
Adler LA, et al. J Clin Psychopharmacol. 2022 Sep-Oct;42(5):429-439.

Post-Hoc Analysis: Centanafadine Improved Executive Dysfunction and Emotional Dysregulation in Adults



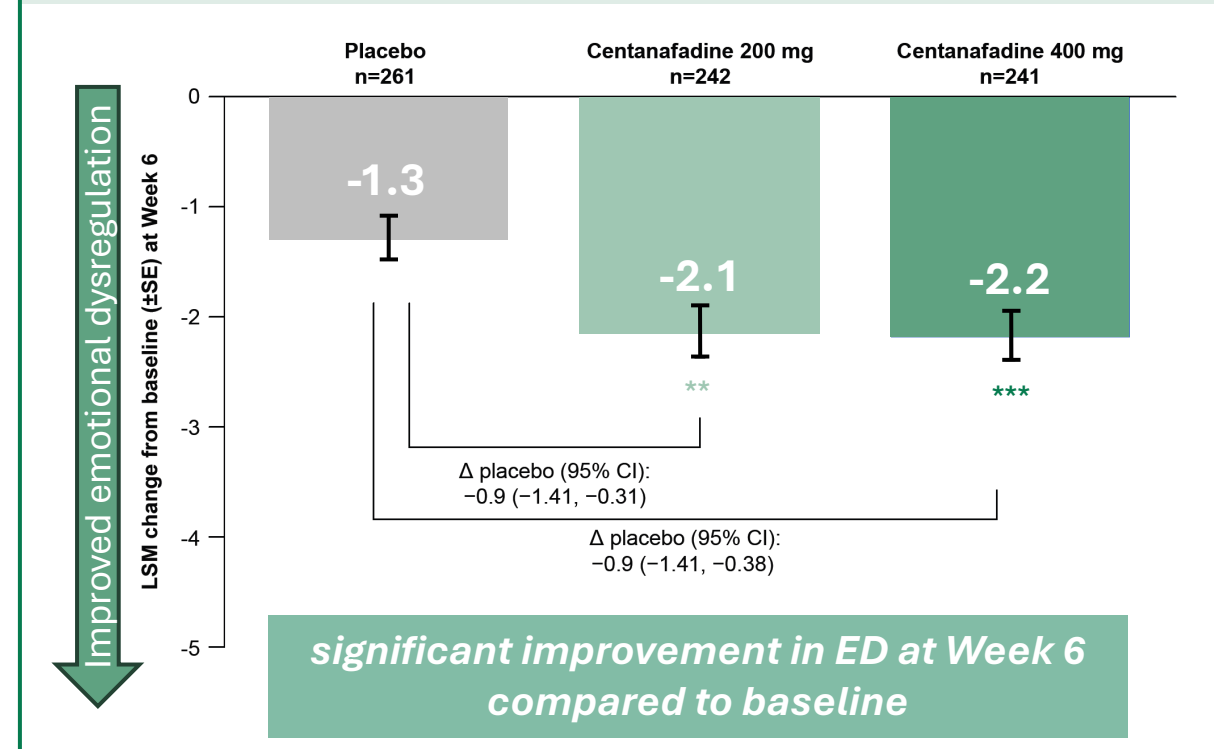
Executive Function

Measured with ASRS Expanded Version Executive Function (EF) subscale



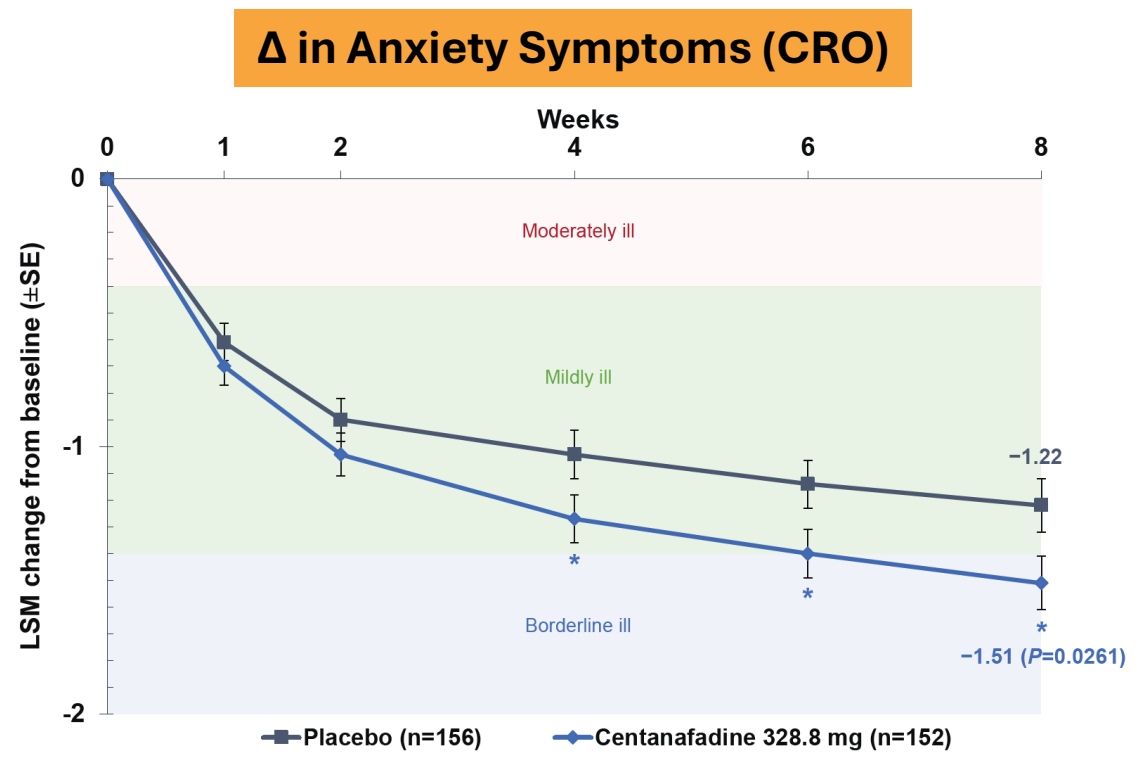
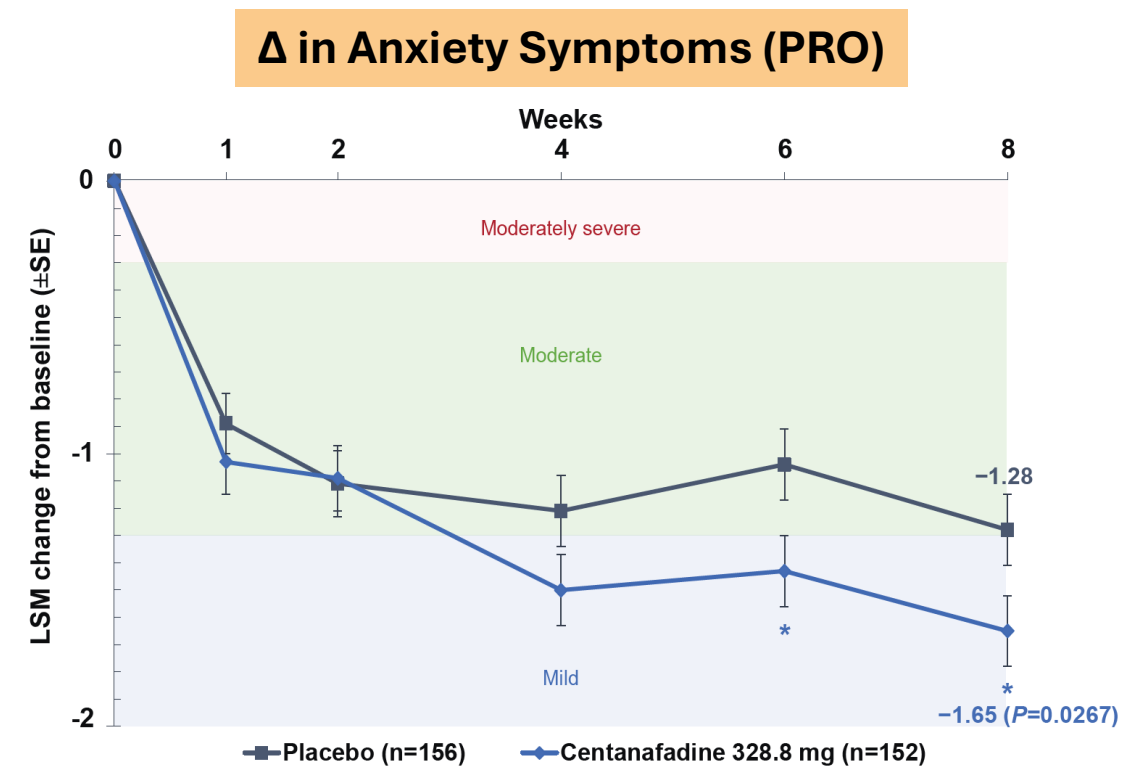
Emotional Dysregulation

Measured with ASRS Expanded Version Emotional Dyscontrol (ED) subscale



** $P < 0.01$, *** $P < 0.001$ versus placebo. ASRS = adult ADHD Self-Report Scale; CI = confidence interval; LSM = least squares mean; SE = standard error. Newcorn JH, et al. Poster #1: Emotional dysregulation symptom outcomes in adults with ADHD treated with centanafadine: a pooled post hoc analysis of two phase 3 trials; Poster #2: Executive function symptom outcomes in adults with ADHD treated with centanafadine: a pooled post hoc analysis of two phase 3 trials. Posters presented at: American Society of Clinical Psychopharmacology (ASCP) Annual Meeting; May 26-29, 2026; Miami, FL.

Centanafadine Improved Clinician- and Patient-Reported Anxiety in Adults with Comorbid ADHD and Anxiety



*P<0.05; Shaded bands indicate approximate CGI-S-anxiety severity categories based on the mean baseline scores and are provided for contextual interpretation of mean change from baseline; they do not represent individual participant shifts in severity.

CRO = clinician-reported outcome; PRO = patient-reported outcome.

Hebert C, et al. Effects of centanafadine on clinician- and patient-rated global impressions in adults with ADHD and comorbid anxiety disorders: a randomized, double-blind, placebo-controlled trial. Poster 216. Presented at Psych Congress 2026; September 15-19, 2026; New Orleans, LA.

Centanafadine Safety and Tolerability



Across age groups, safety and tolerability were **generally favorable**



In children (6-12yo), ~**37%** of participants treated with centanafadine experienced an AE

- Most common: decreased appetite, rash, fatigue, and abdominal pain



In adolescents (13-17yo), ~**41%** of participants treated with centanafadine experienced an AE

- Most common: decreased appetite, nausea, headache, and rash



In adults (18-55yo), **41.1%** of participants receiving centanafadine experienced a TEAE

- Most common: headache, decreased appetite, insomnia, and nausea

AE=adverse event; TEAE=treatment-emergent adverse event.

Ward CL, et al. *Pediatr Open Sci.* 2025;1(3):1-11; Ward CL, et al. *J Am Acad Child Adolesc Psychiatry.* Published online July 4, 2025; Adler LA, et al. *J Clin Psychopharmacol.* 2022 Sep-Oct;42(5):429-439.

Key Learning Points

- Traditional stimulant therapies remain highly effective for ADHD but may be limited by tolerability concerns, misuse or diversion risk, effects on sleep and appetite, and co-occurring psychiatric conditions.
- Non-stimulant therapies, including atomoxetine, alpha-2 agonists, viloxazine ER, and off-label bupropion, provide alternative mechanisms that may better align with individual symptoms, comorbidities, and treatment needs.
- Centanafadine's novel MOA (inhibiting norepinephrine, dopamine, and serotonin reuptake) targets three monoaminergic systems involved in attention, motivation, and emotional regulation.
 - In pooled post hoc analyses of two Phase 3 trials, both doses of centanafadine were associated with improvements in patient-reported executive dysfunction and emotional dysregulation, in addition to core ADHD symptoms.



Features Out of Focus:
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Thank You!

