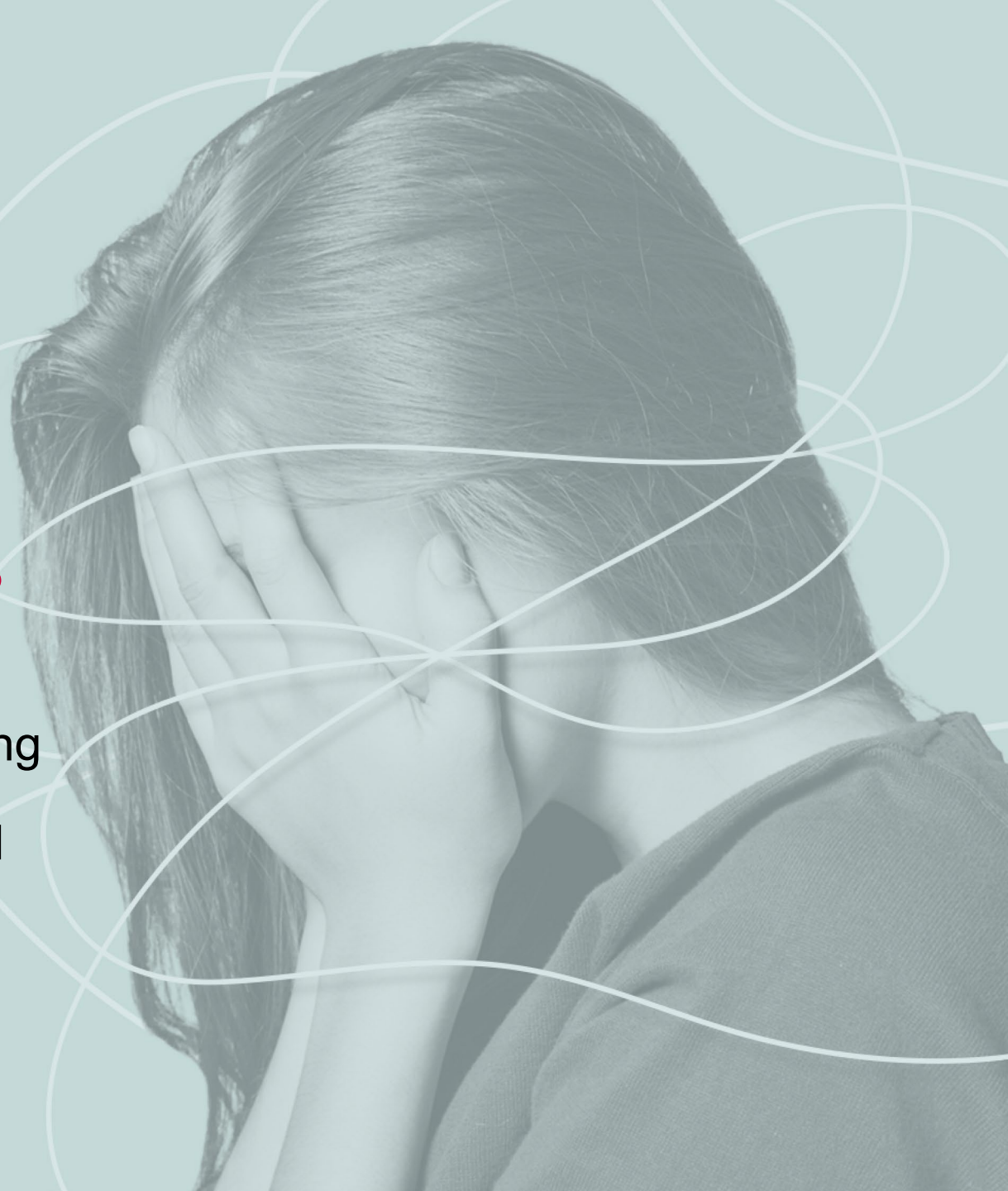
Module 3: Clinical Evidence for Emerging Pharmacologic Strategies

Learning Objective:

Evaluate novel pharmacologic targets involving serotonergic modulation as emerging strategies to address under-recognized and under-treated features of ADHD



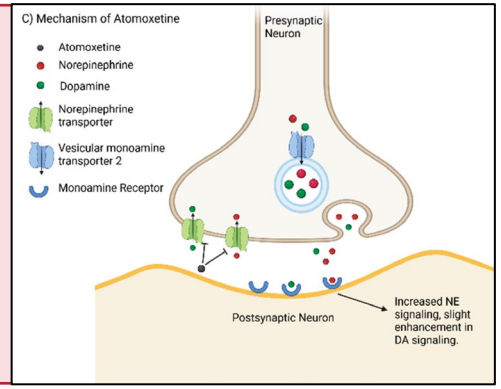
Current Availability of Nonstimulant ADHD Medications

- **Nonstimulants**
  - **Not FDA Approved**
    - **Historical**: TCAs, modafinil/armodafinil, bupropion
    - **In development**: centanafadine, solriamfetol
  - **FDA Approved**
    - Atomoxetine
    - Alpha 2 agonists (clonidine XR and guanfacine XR)
    - Viloxazine ER

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 (WIFRS), Quality of Life (CHQ, AAQoL), Executive function (BRIEF), Oppositionality (CPRS), Emotional lability (WRAADDS), Anxiety (PARS, LSAS), but NOT for depression

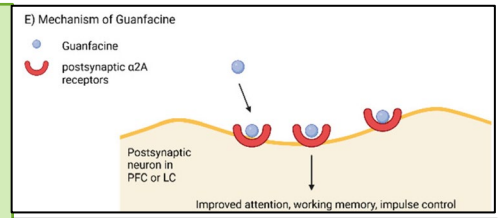


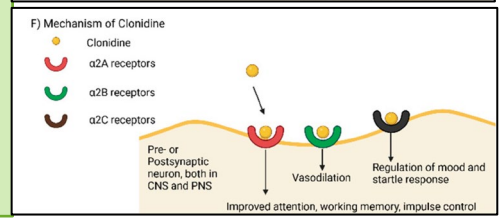
MOA: agonism of noradrenergic alpha 2A (presynaptic) and 2C (postsynaptic) receptors

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?

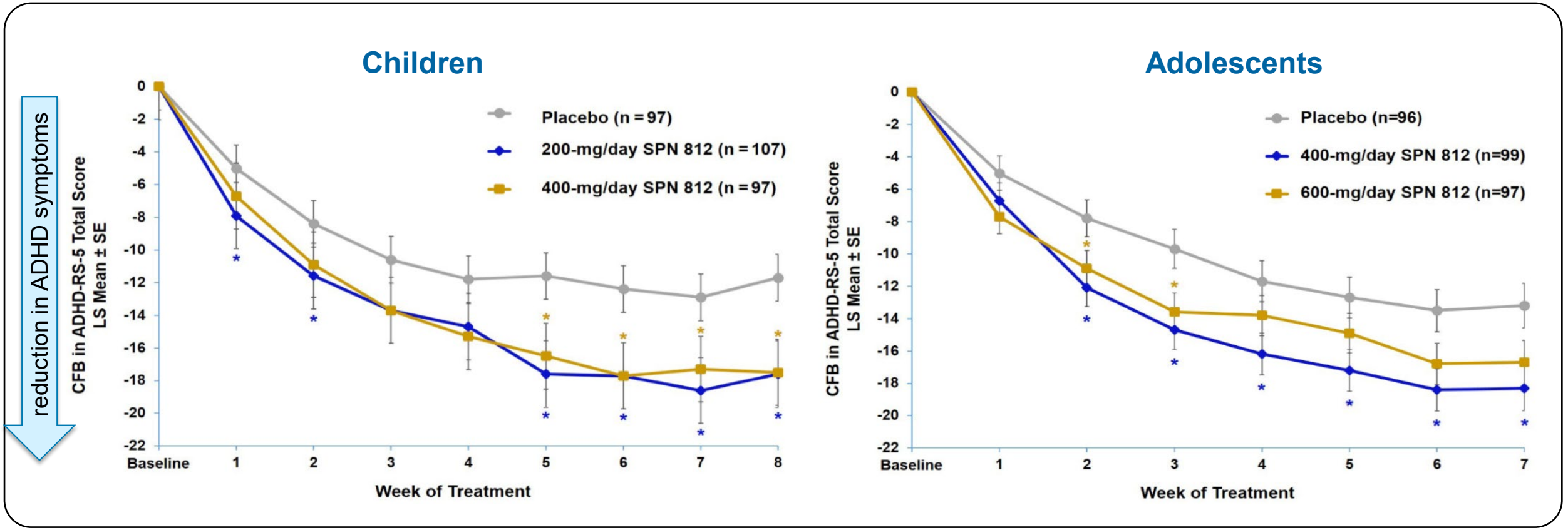




AAQoL=Adult ADHD QoL Measure; BRIEF=Behavior Rating Inventory of Executive Function; CHQ=Children’s Health Questionnaire; CPRS=Conners Parent Rating Scale; LSAS=Liebowitz Social Anxiety Scale; MOA=Mechanism of action; PARS=Pediatric Anxiety Rating Scale; WIFRS=Weiss; WRAADDS=Wender-Reimherr Adult Attention Deficit Disorder Scale

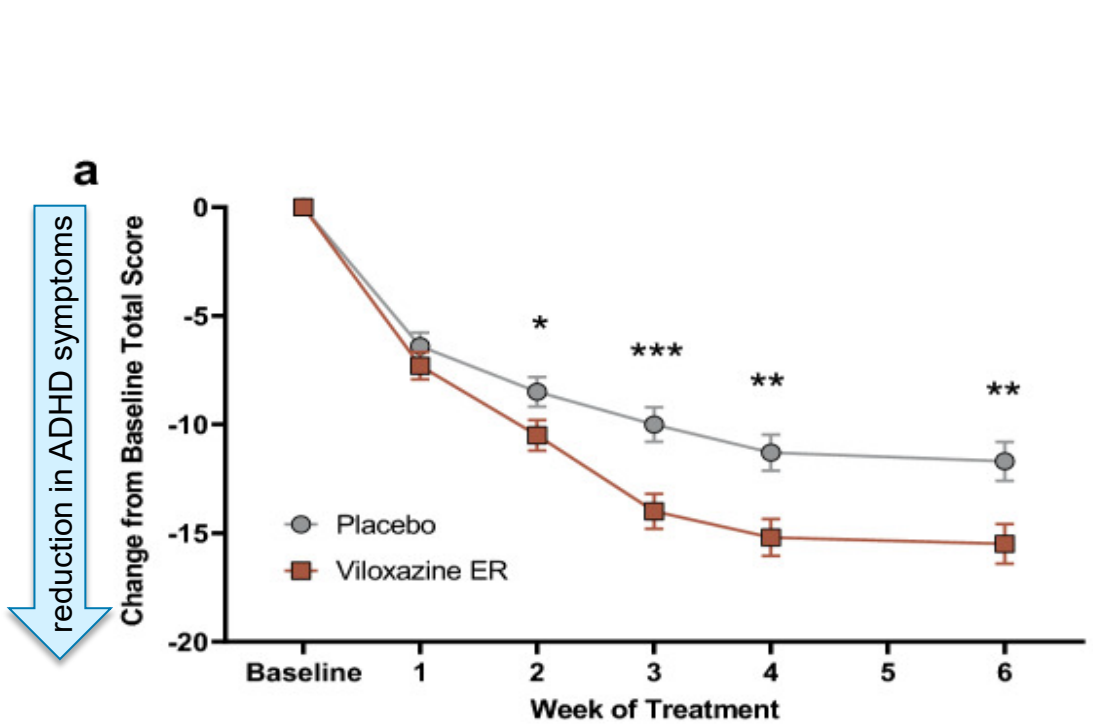
Childress AC. Therapeutics and Clinical Risk Management 2016:12 27–39. Schwartz S and Correll C. J Am Acad Child Adolesc Psychiatry. 2014 Feb;53(2):174-87.Bellato A, et al. J Am Acad Child Adolesc Psychiatry 2025;64(3):346-361. Sallee FR. Postgrad Med. 2010 Sep;122(5):78-87. Ming X, et al. Adolesc Health Med Ther. 2011 Sep 30;2:105–112. Yacoub MW, et al. Cells. 2025;14(17):1367

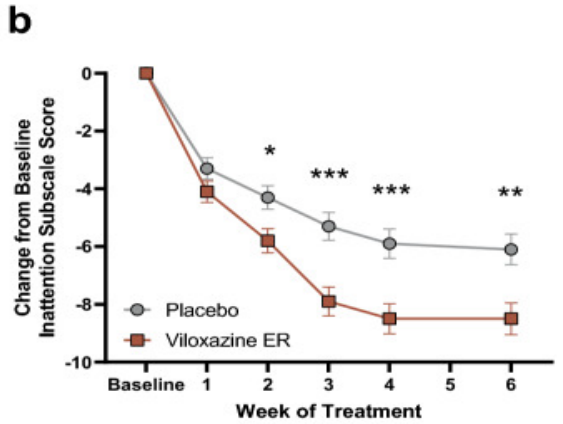
Viloxazine ER Efficacy: Children & Adolescents

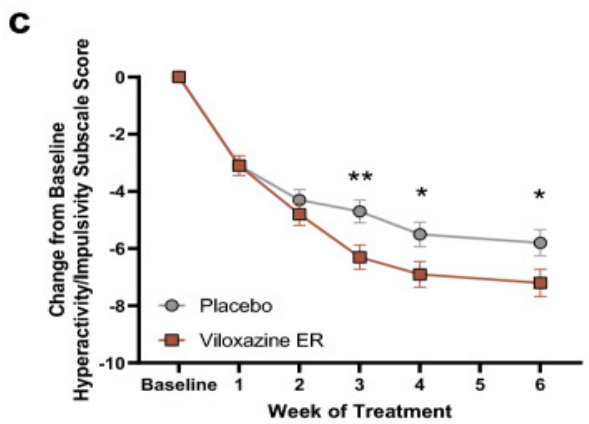


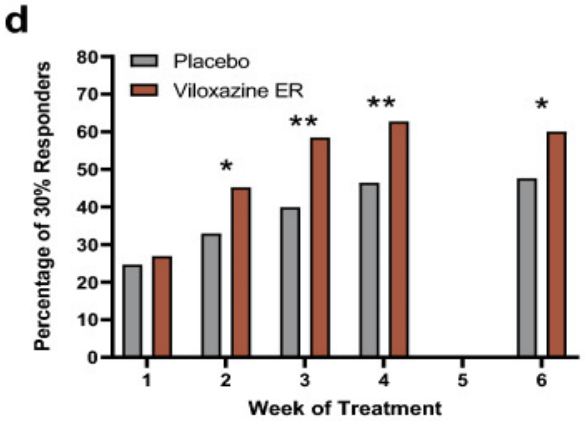
Nasser A, et al. Clin Ther. 2021;43(4):684-700; Nasser A, et al. Psychopharmacol Bull. 2021;51(2):43-64. Nasser et al. The Efficacy and Safety of SPN-812 (Viloxazine Extended-Release) for the Treatment of ADHD in Children and Adolescents. NEI Virtual Meeting 2021

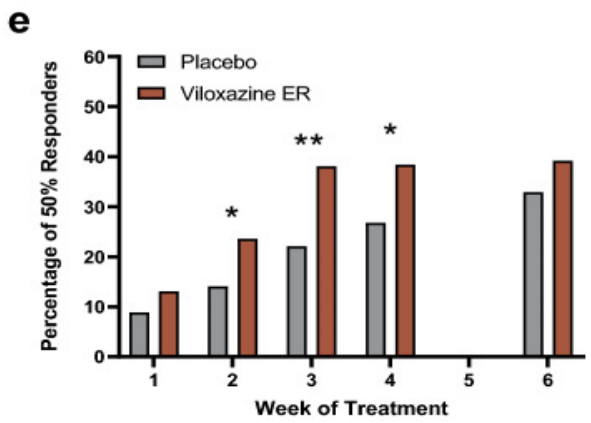
Viloxazine ER for Adult ADHD







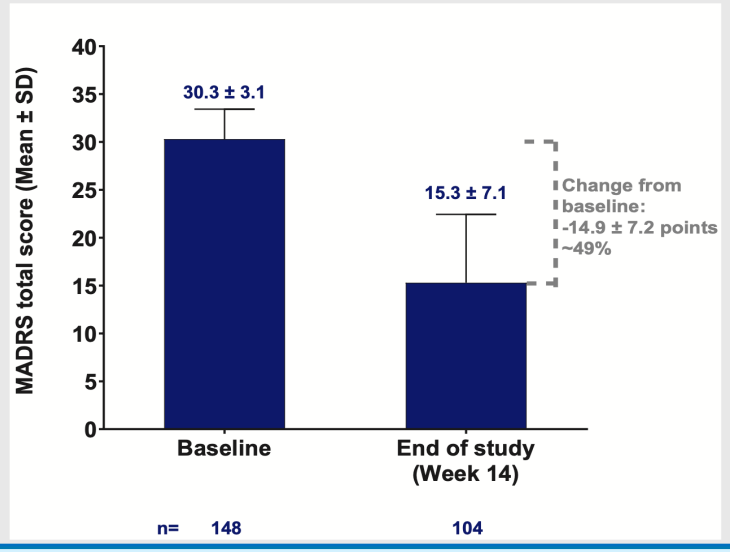




Nasser A, et al. CNS Drugs. 2022 Jul 27;36(8):897–915.

Viloxazine ER for Depression and Anxiety in ADHD

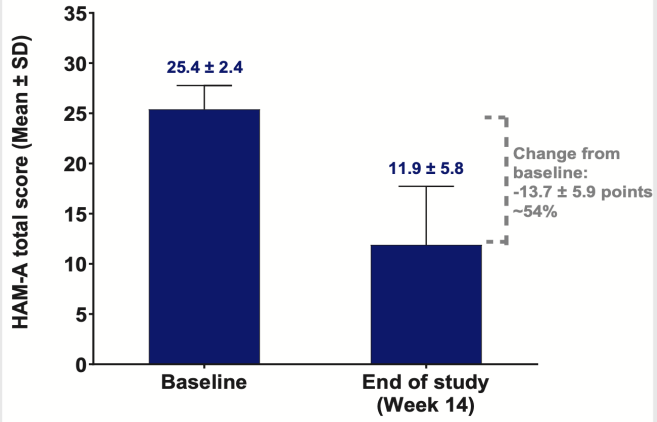
MADRS (ClinRO)



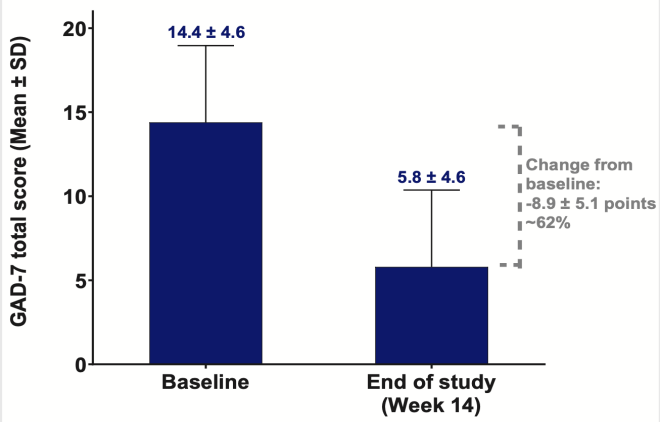
Clinician-rated depressive symptom scores showed **~49% improvement from baseline to Week 14**

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

HAM-A (ClinRO)



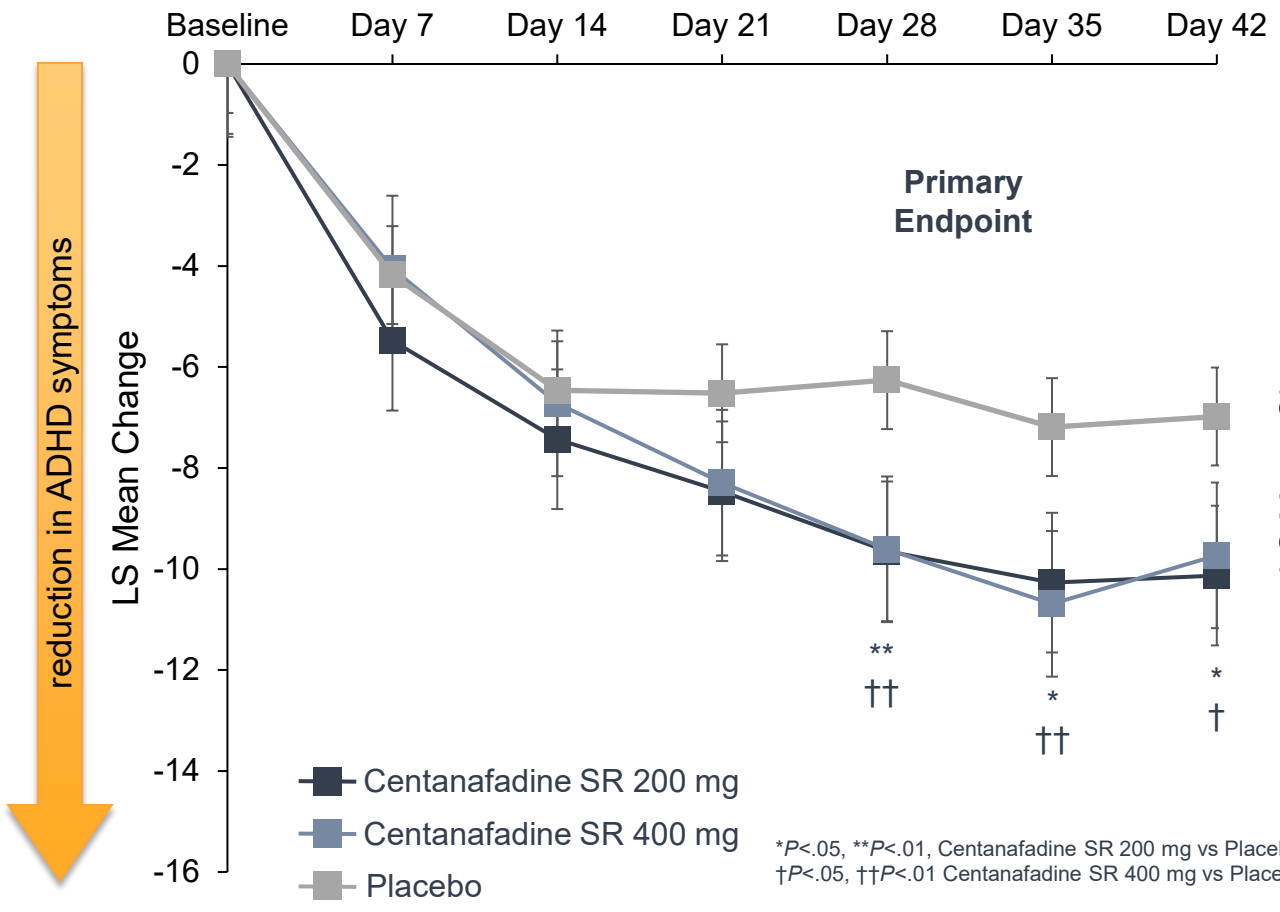
GAD-7 (PRO)



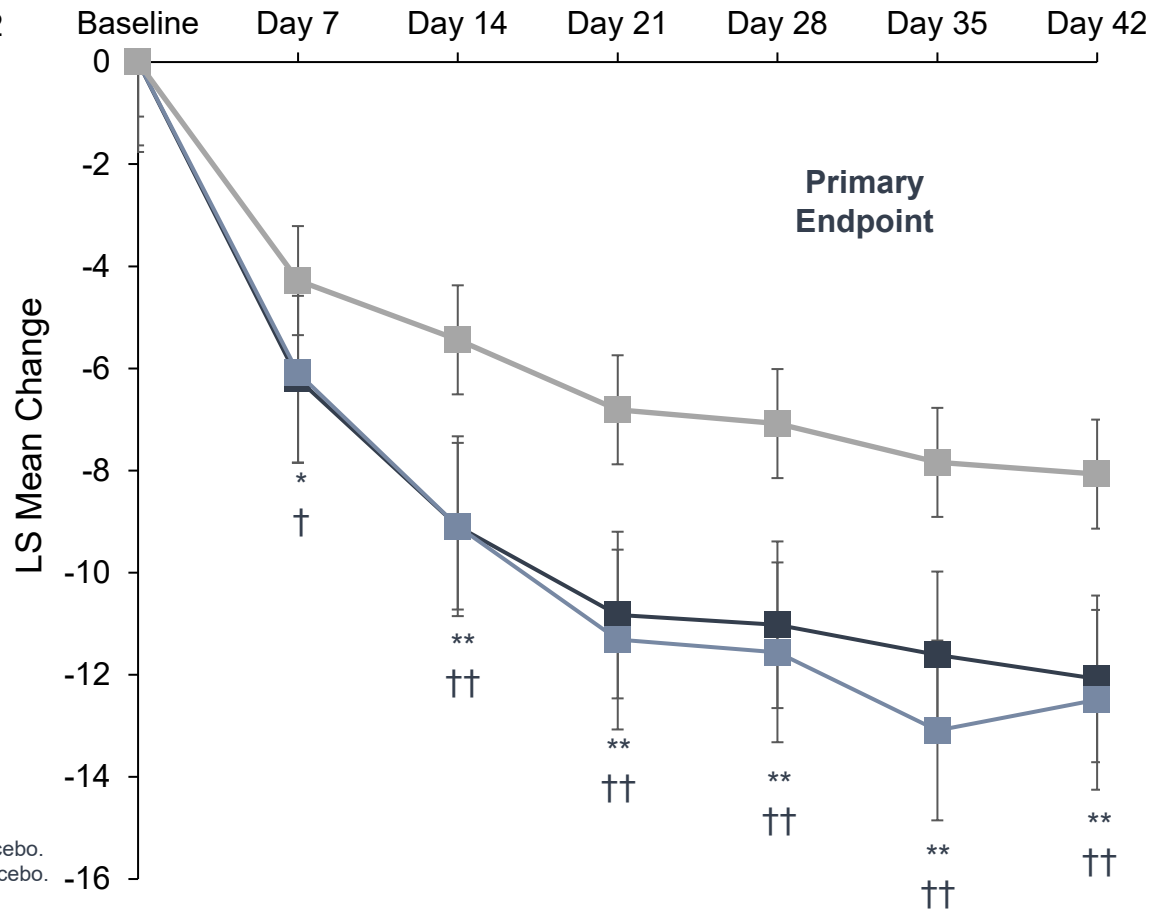
Adler L, Mattingly GW, et al. Nevada Psychiatric Association Meeting, Las Vegas, NV, Feb 2025 (Poster)

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

Study 1



Study 2



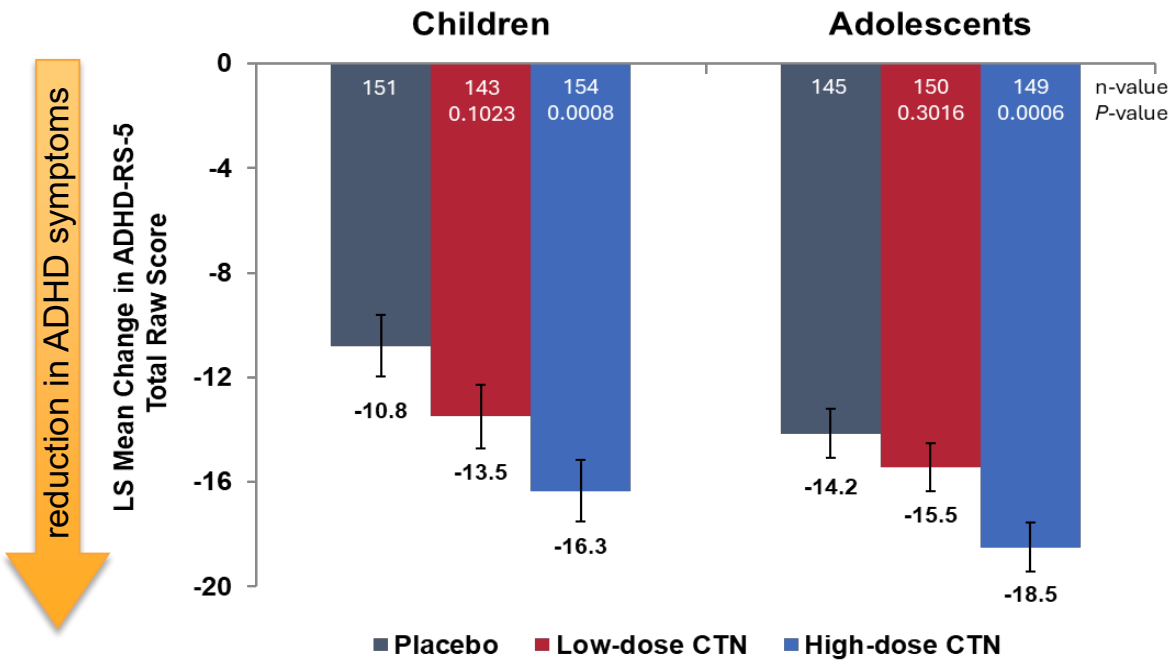
AISRS=ADHD Investigator Symptom Rating Scale; LS=least squares; MMRM=Mixed Models for Repeated Measures; SR=sustained release.

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

Centanafadine XR 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

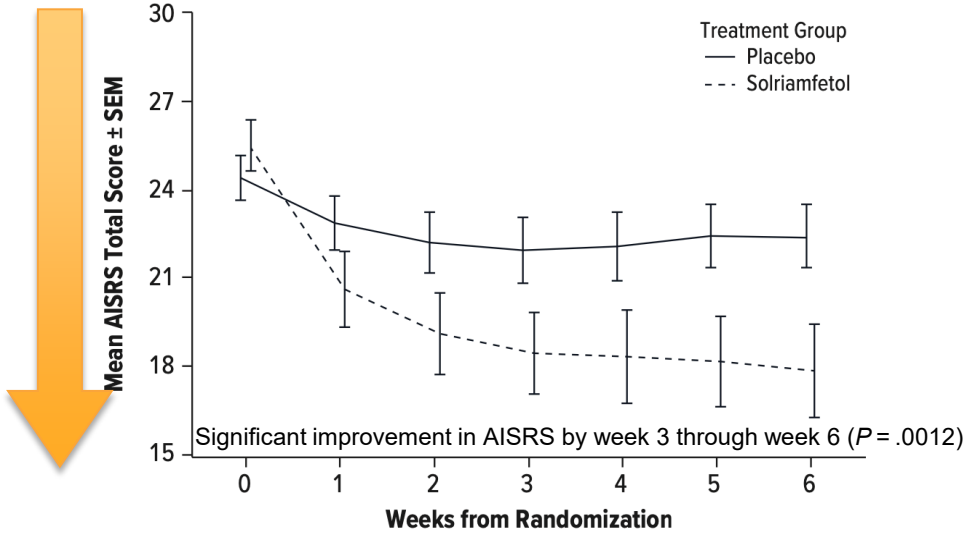
Adolescents
Low Dose: 164.4mg
High Dose: 328.8mg

Ward et al., Efficacy and Safety of Once-Daily Extended Release Centanafadine for the Treatment of Attention-Deficit/Hyperactivity Disorder in Pediatric Patients. Poster presented at the NEI Congress 2024; November 7-10, 2024 (Colorado Springs, CO)

Solriamfetol

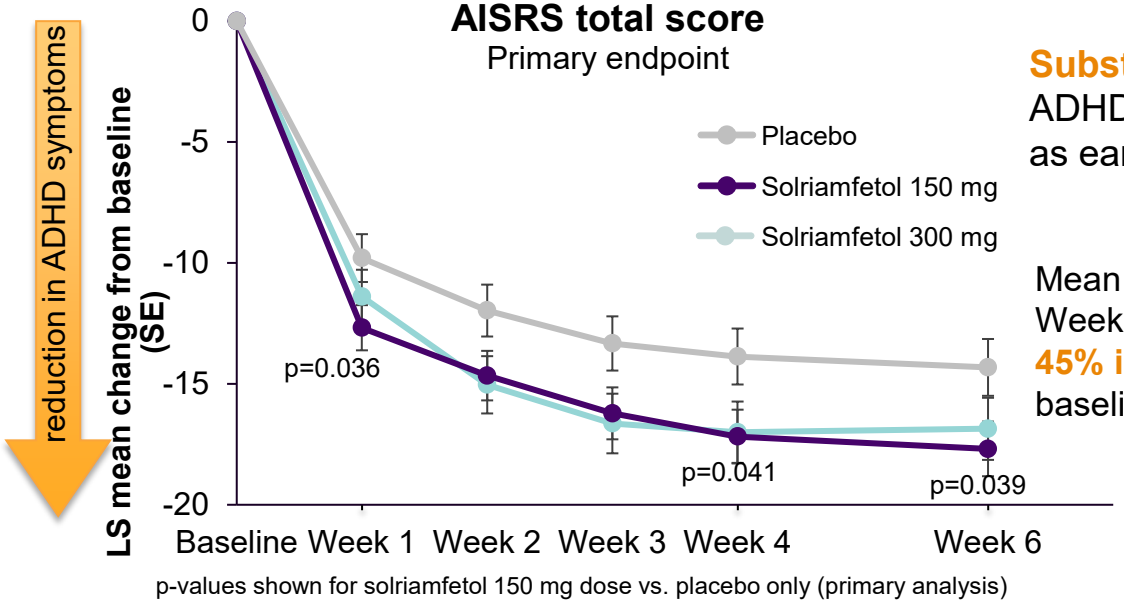
- **MOA**: Potent DNRI and 5HT1A and TAAR1 agonist
- FDA approved in March 2019 for EDS associated with narcolepsy or OSA

Double-blind Pilot Study (N=60 adults)



Remotely conducted, randomized, double-blind, placebo-controlled, dose-optimization trial of 75 mg or 150 mg.

FOCUS Phase III Study in Adults with ADHD



p-values shown for solriamfetol 150 mg dose vs. placebo only (primary analysis)

Substantial improvement in ADHD symptoms observed as early as Week 1

Mean reduction in AISRS at Week 6 represents a **45% improvement** from baseline in ADHD symptoms

DNRI=Dopamine-Norepinephrine Reuptake Inhibitor; TAAR1=Trace Amine-Associated Receptor-1; EDS=Excessive Daytime Sleepiness; OSA=Obstructive Sleep Apnea.

Surman CBH, et al. J Clin Psychiatry 2023;84(6):23m14934; Data on file, Axsome Therapeutics. Used with permission from Axsome Therapeutics. Frontiers in Brain Health R&D Day. https://axsometherapeuticsinc.gcs-web.com/static-files/c9a3a0a7-cd82-4e73-8a2b-ccb6a41c8214. Accessed 1.15.26.