Pharmacological Treatment of ADHD Across the Life Span: Nonstimulants

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PSYCHIATRY ACADEMY

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Disclosures

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Dr. Spencer receives royalties from Cambridge University Press for book publication

Dr. Spencer receives support from Royalties and Licensing fees on MGH copyrighted ADHD scales through MGH Corporate Sponsored Research and Licensing.

Dr. Spencer has a US patent (#14/027,676) for a nonstimulant treatment for ADHD (no license fees), and has a patent pending (#61/233,686) for a method to prevent stimulant abuse (no license fees). Both through MGH corporate licensing

Non-Stimulants: When to Use

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T Wilens

- Monotherapy
  - smaller ES than stimulants
- Stimulant Issues
  - nonresponders
  - Stimulant partial responders
    - monotherapy,
    - adjunctive therapy; no drug interactions with stimulants
  - Adverse effects to stimulants
  - Concerns of stimulant diversion
- Comorbid ADHD plus
  - Oppositional disorder / Emotional dysregulation
  - Anxiety
  - Tics
  - Substance abuse
  - Persistent Exe Fx impairments

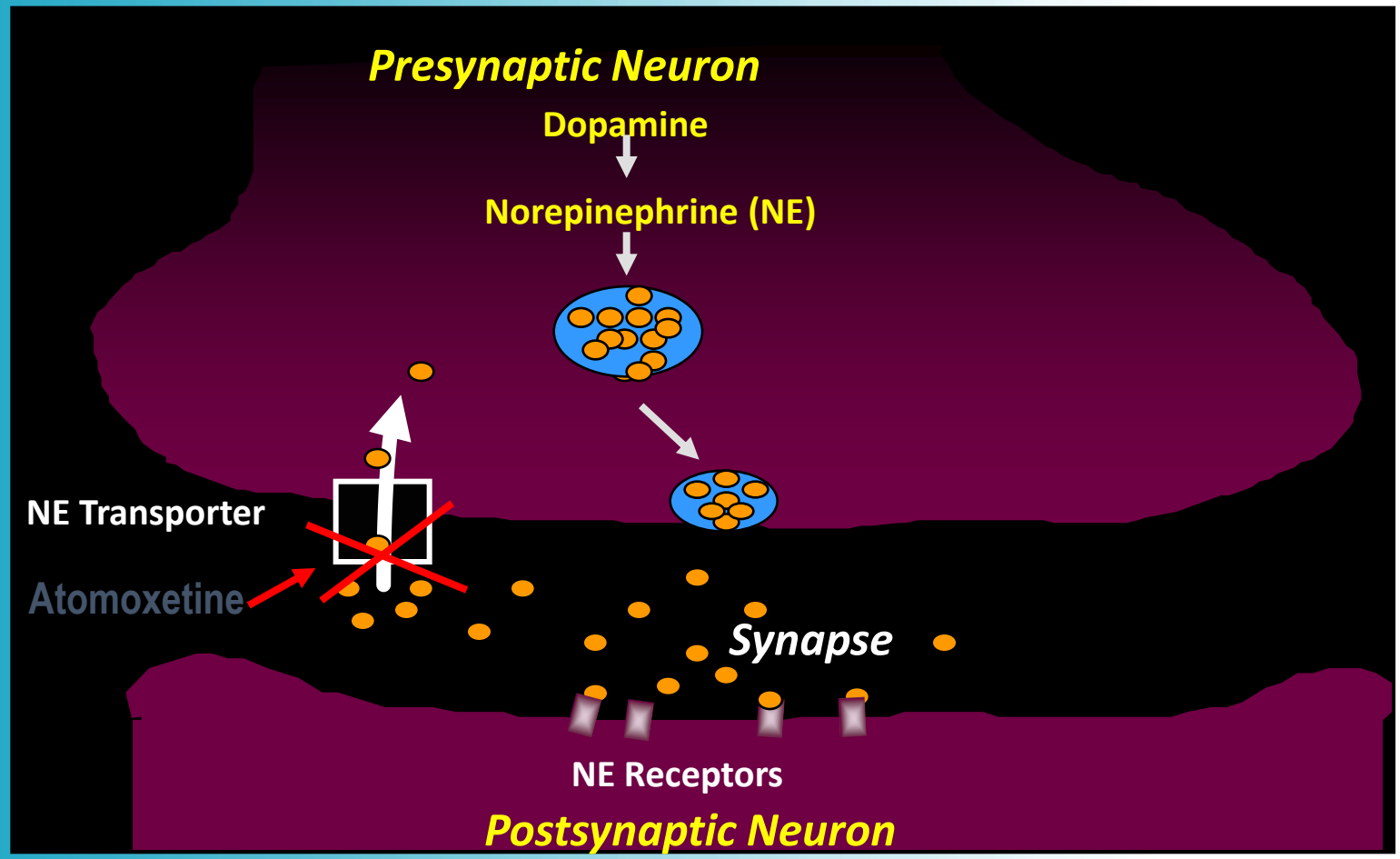
Prefontal Cortex and ADHD

Right dorsal prefrontal cortex lesions have deficits in sustaining attention regulation and inhibiting responses to distracting stimuli

Right orbital prefrontal cortex lesions have deficits in affective realm, immature behavior, lack of restraint and increased motor activity

Arnsten et al. *AGP.* 1996

Atomoxetine*
Mechanism of Action



*FDA approved for ADHD.

Clinical Responses to Atomoxetine

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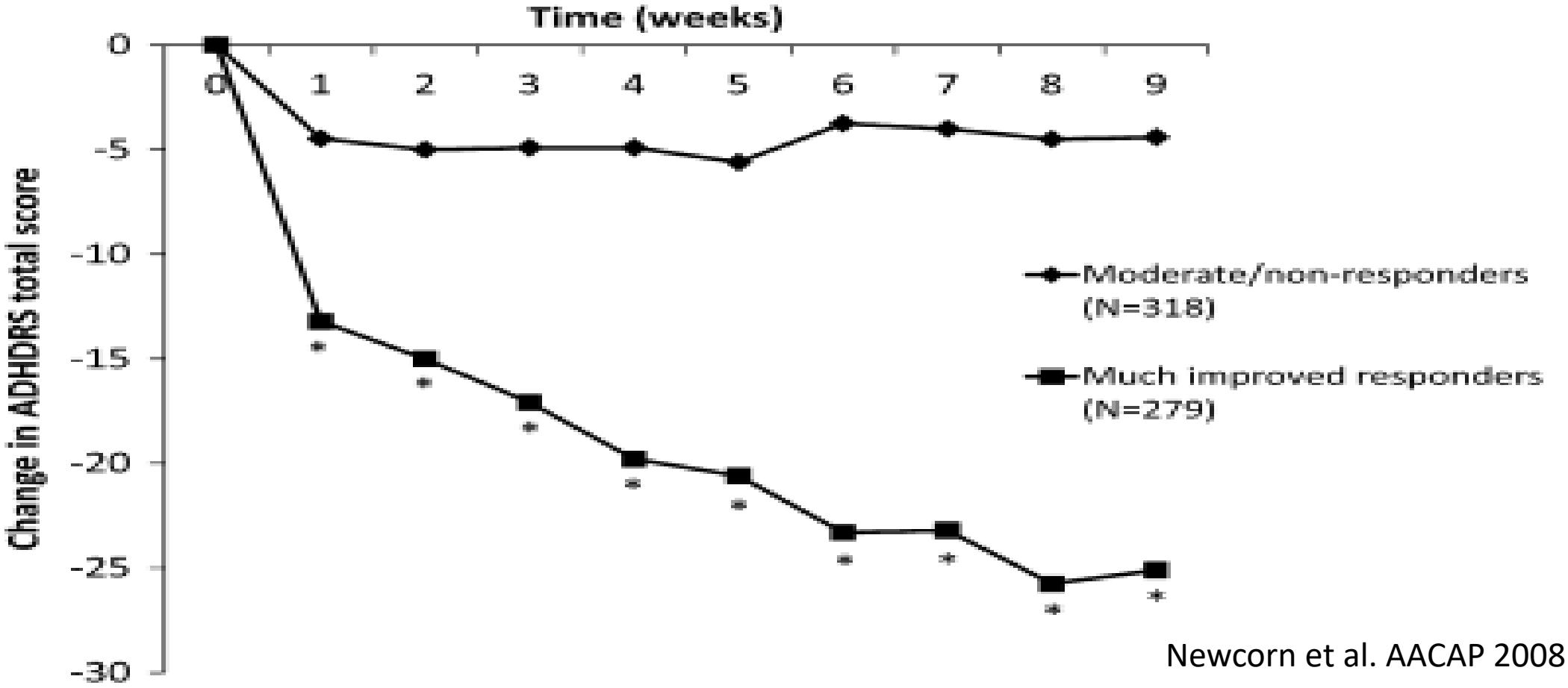

Newcorn et al. AACAP 2008

Fig. 1 Temporal course of changes in the Attention-Deficit/Hyperactivity

Atomoxetine for Youth with ADHD & Anxiety

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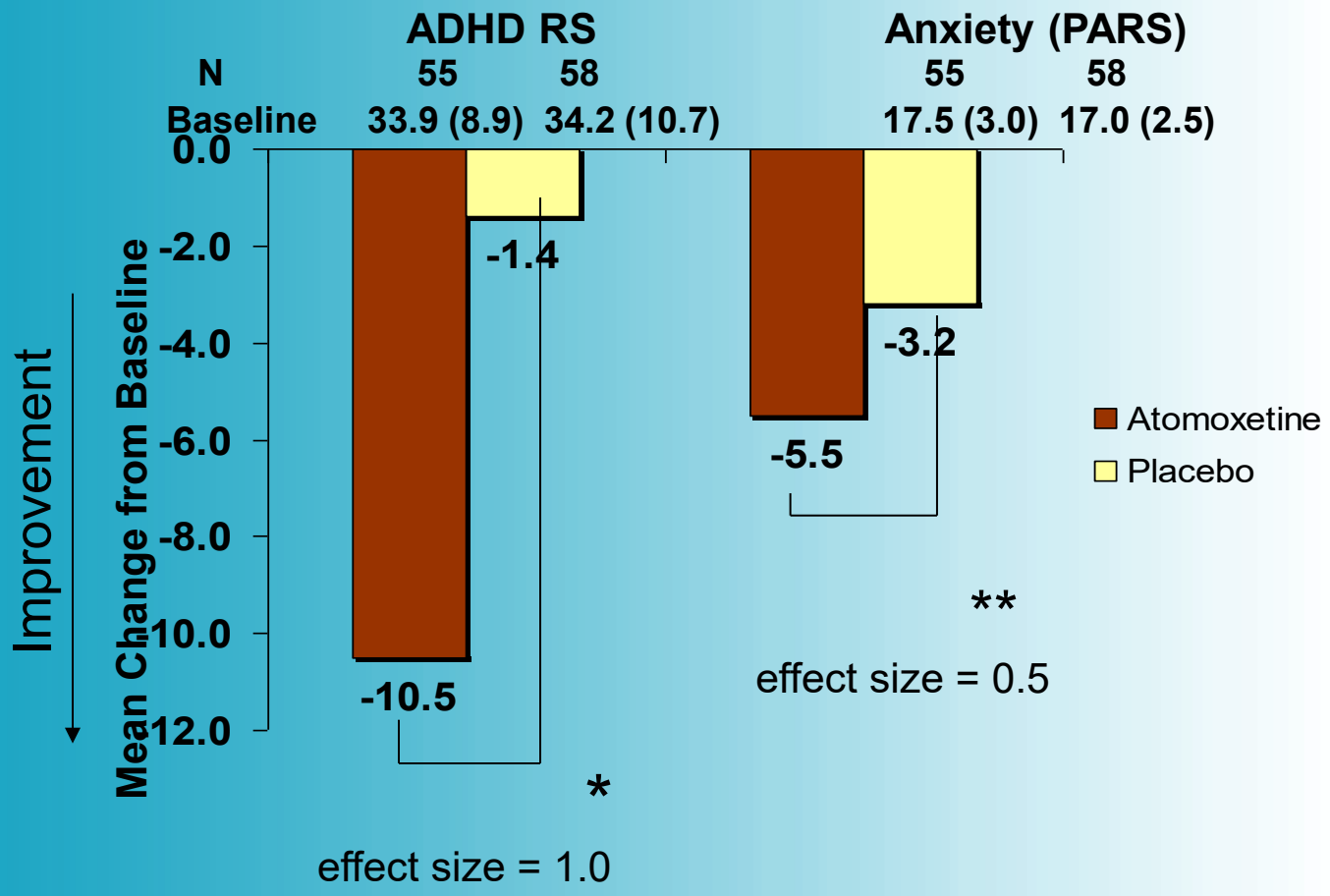


* p<.001

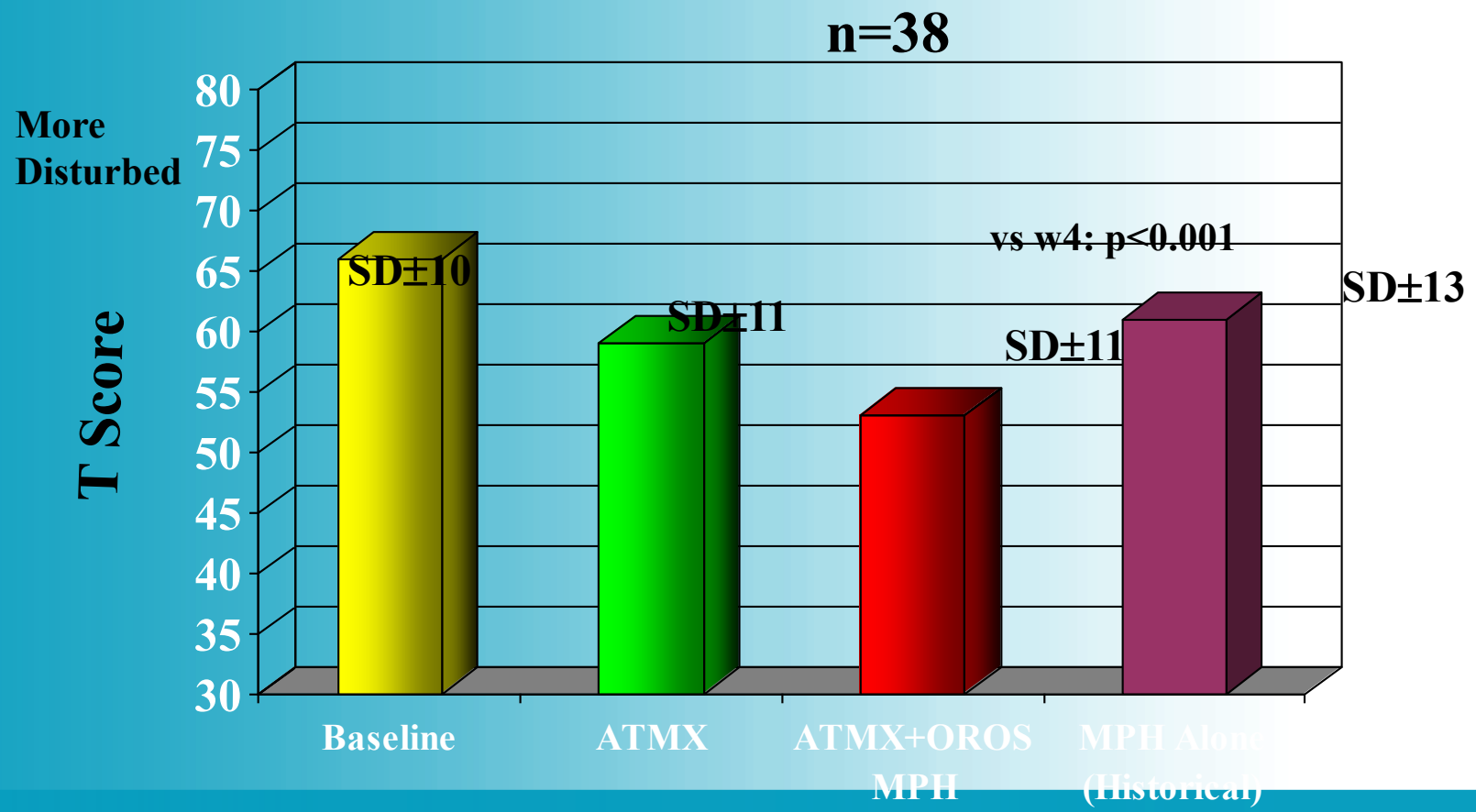
** p=.011

Dose of ATMX = 1.26 mg/kg/day

(Geller et al. JAACAP 2007)

OROS MPH plus ATMX*: Improvement Characterized by the BRIEF: Initiation

Results



*Not FDA approved for ADHD

(Wilens et al. J Child Adolesc Psychopharm: 2009)

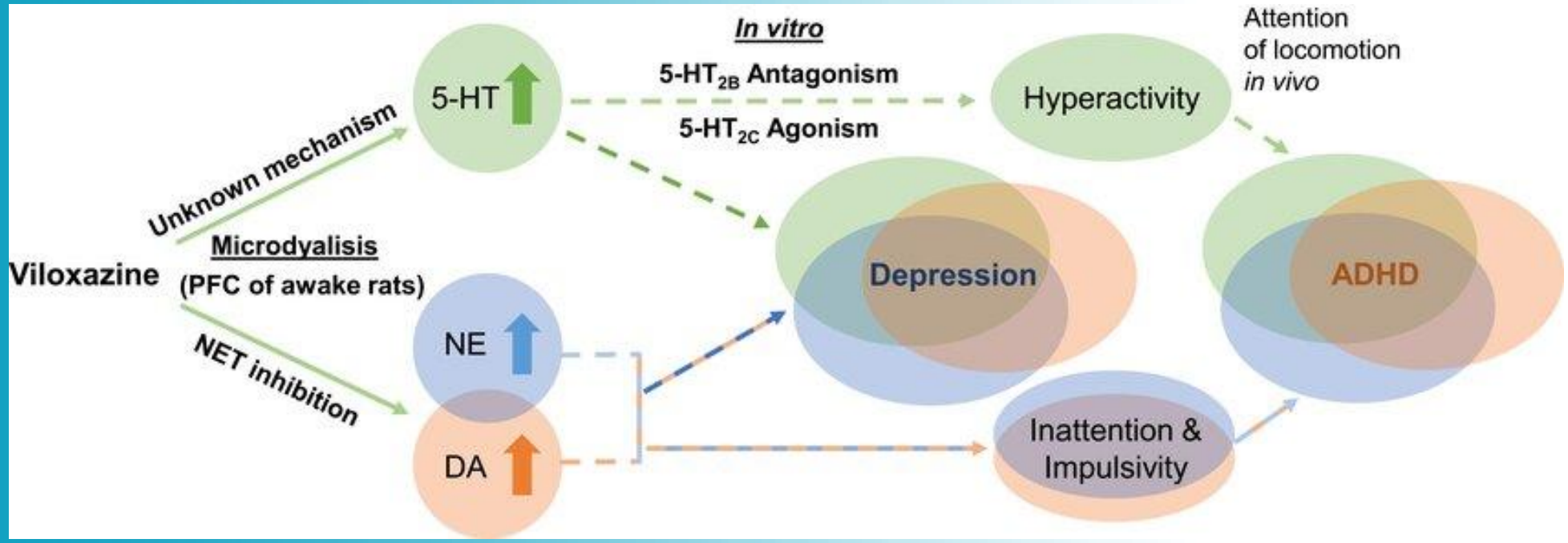
Atomoxetine

- Adverse effects:
  - Rare hepatic injury (2 cases): advise, LFTs NOT required
  - Suicidality (0.37% vs 0%): black box
  - Somnolence, appetite suppression, GI upset/dyspepsia, blood pressure/pulse, sexual dysfunction (adults), irritability
  - Potential drug interactions (lower dose if using with p448 inhibitor and vice versa)

- Dosing (Wilens' method):
  - Start at 0.5 mg/kg/day for two weeks, then increase to 1.2 mg/kg/day.
  - Treat to 4 weeks, if no response, try another agent. If response, maintain dose for 6-10 weeks then reevaluate
  - After 6-10 weeks if partial response, increase to 1.8-2 mg/kg/day
  - FDA approved up to 1.4 mg/kg max 100 mg/day

- Dosing (TS method) BiD=>QD decrease GI sxs

Viloxazine
Proposed dual mechanism of action



Yu C J of Experimental Pharmacology 2020

Viloxazine XR for ADHD

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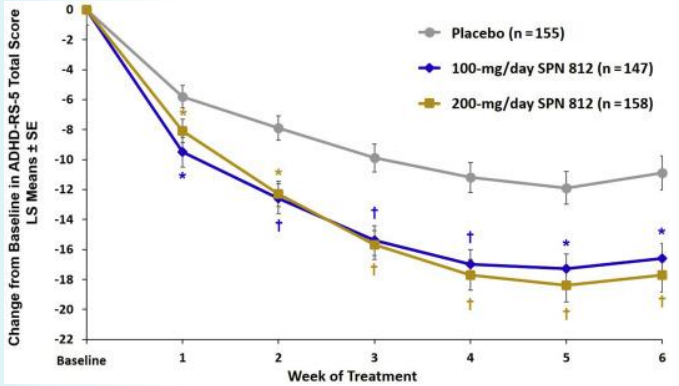
- **Noradrenergic reuptake inhibitor; Serotonin modulating agent**
  - **5-HT 2B antagonist, 5-HT 2C partial agonist)**
  - **Increases NE, DA, 5HT in PFC**
- **Approved in children, adolescents, and adults**
- **Phase III, 6 week RCT study**
- **N = 444 children with ADHD**
- **[Positive trials in adolescents and adults]**

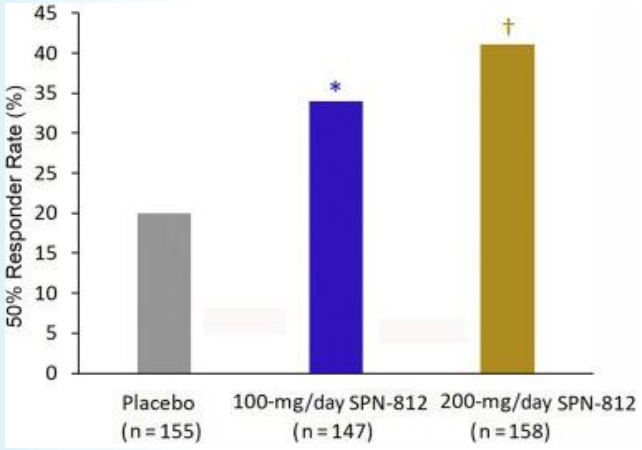
Findings

- **Improvement in 100 and 200 mg doses**
- **ADHD RS, Weiss Functional Scale, CGI**
- **Improvement noted at week 1**

Side effects

- **Somnolence, decreased appetite, headache**





Nasser et al. *Clin Ther.* 2020:42(8):1452-1466.

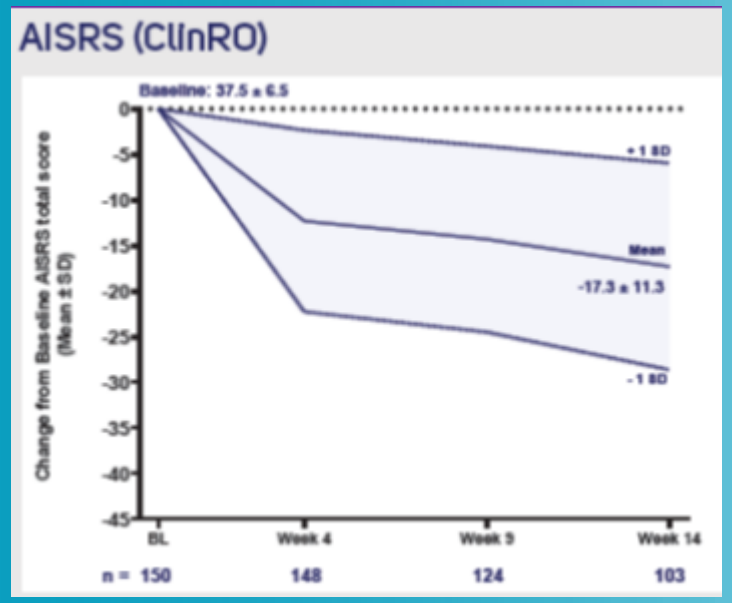
Viloxazine XR for ADHD

- **FDA approved Prescribing Information:**
  - **Children: start with 100 mg x 1 week, then increase to 200 mg/day up to 400 mg**
  - **Adolescents: Start with 200 mg x 1 week, then increase to 400 mg/day;**
  - **Adults up to 600 mg**
  - **Titration hints: may slow increase, qHS dose**
- **Viloxazine is a strong CYP1A2 inhibitor. Concomitant use of viloxazine significantly increases the total exposure, but not peak exposure, of sensitive CYP1A2 substrates,**
- **Increased risk of adverse reactions associated with these CYP1A2 substrates.**
- **Coadministration with viloxazine XR is contraindicated. Examples Alosetron, duloxetine, ramelteon, tizanidine, theophylline**
- **Careful with caffeine**
- **Unclear effect on melatonin**
- **BLACK BOX Suicidality**

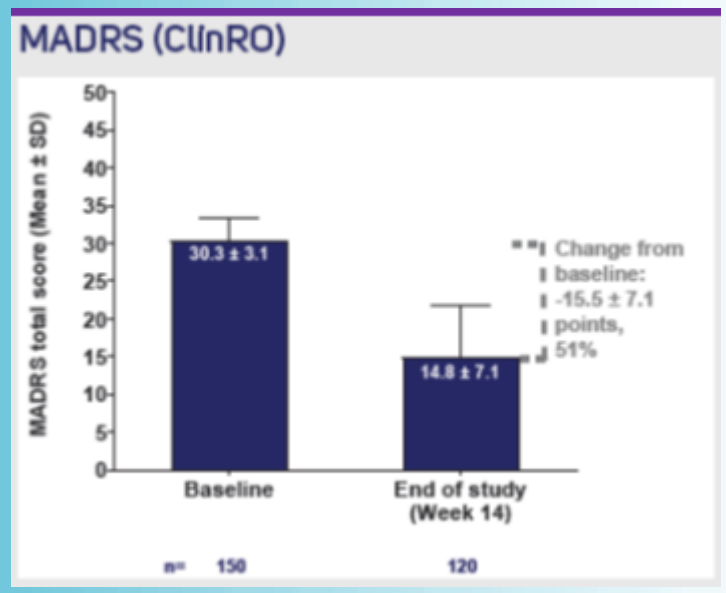
Viloxazine ER Open Adult Trial ADHD Mood/Anxiety

- Selective NE re-uptake inhibitor with pre-clinical 5-HT effects, approved for ADHD
- Decentralized trial with trained raters- different from RCT- reporting

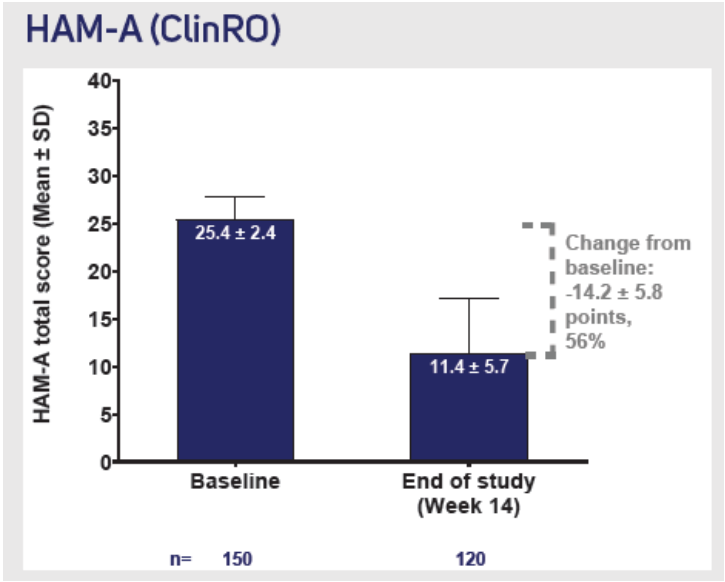
- 15 weeks of viloxazine 200 -600 mg/day n=161



ADHD



Mood



Anxiety

Adler LA et al. Presented at APA Annual Meeting 2025

Alpha Agonists: Clonidine & Guanfacine

(Arnsten and Li, Biol Psych 2005; Wilens J Clin Psych 2006)

- Alpha agonist agents
  - Mimics Norepinephrine at alpha receptors
  - Presynaptic Alpha 2a (inhibitory)
  - Post synaptic alpha 1, 2 a-c (alpha 2a in PFC)
    - (guanfacine more specific)

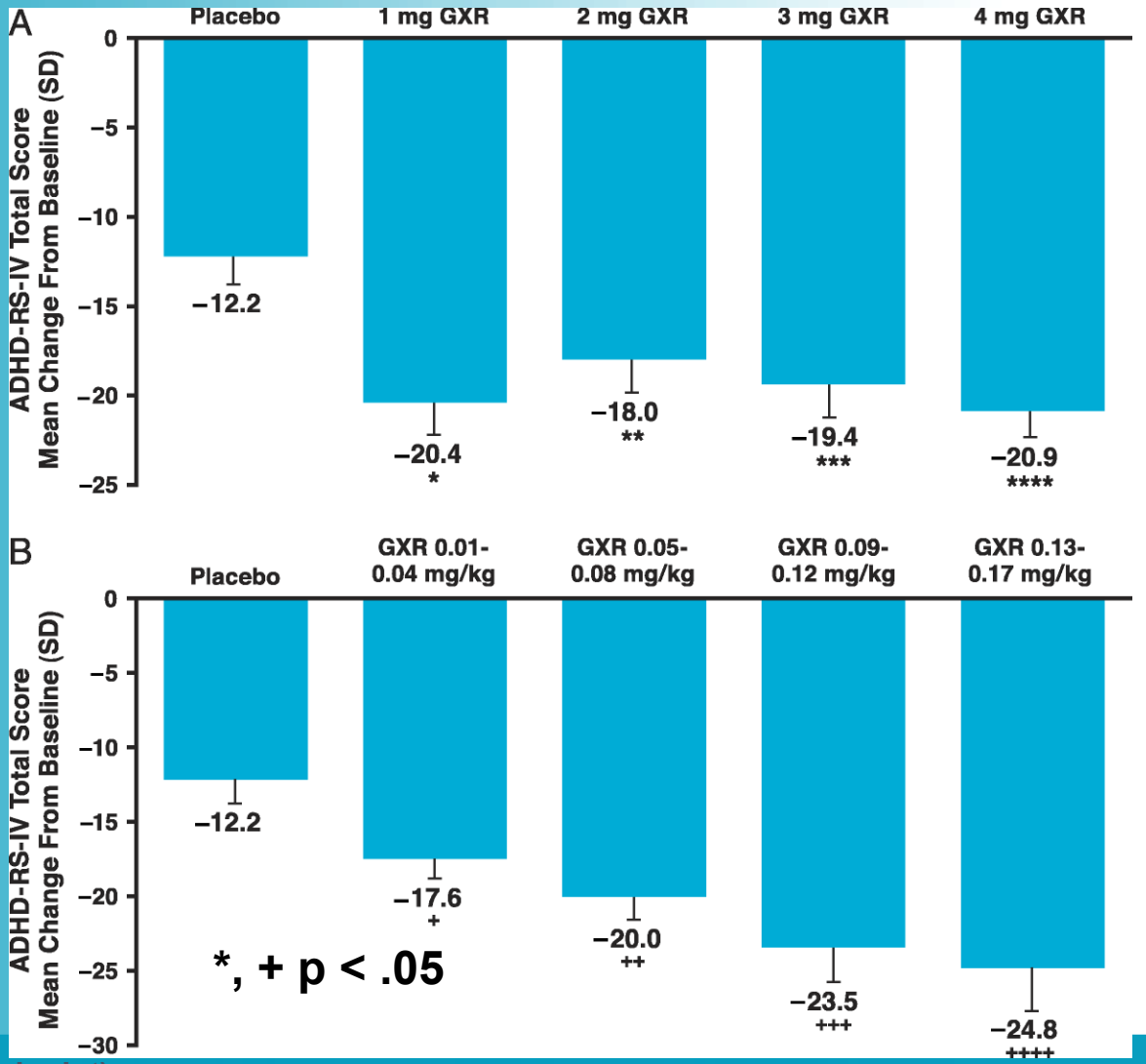
- Effect on Prefrontal cortex (PFC)
  - Improves PFC blood flow and functioning in animal models

- Effect on Locus Coerulus (down regulate sympathetic nervous system)
  - Repurposed anti-hypertensives

- Modulate of neurotransmission of other neuronal systems (glutamate, GABA, cholinergic, opioid)

Guanfacine Extended-Release in ADHD

(N = 324 [51 sites]; 6 weeks active*, mean age 11 ± 3 yrs)



Effect size:
0.41-0.89

*3 weeks titration
3 weeks maintenance (endpoint)
3 weeks taper

Sallee et al. J AM Acad Child Adolesc Psychiatry. 2009;48:155-165.

Guanfacine XR in Adolescent ADHD: Higher Doses Maybe Necessary

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Objective

Despite the continuity of attention-deficit/hyperactivity disorder (ADHD) into adolescence, little is known regarding use of nonstimulants to treat ADHD in adolescents. This phase 3 trial evaluated the safety and efficacy of guanfacine extended release (GXR) in adolescents with ADHD.

Method

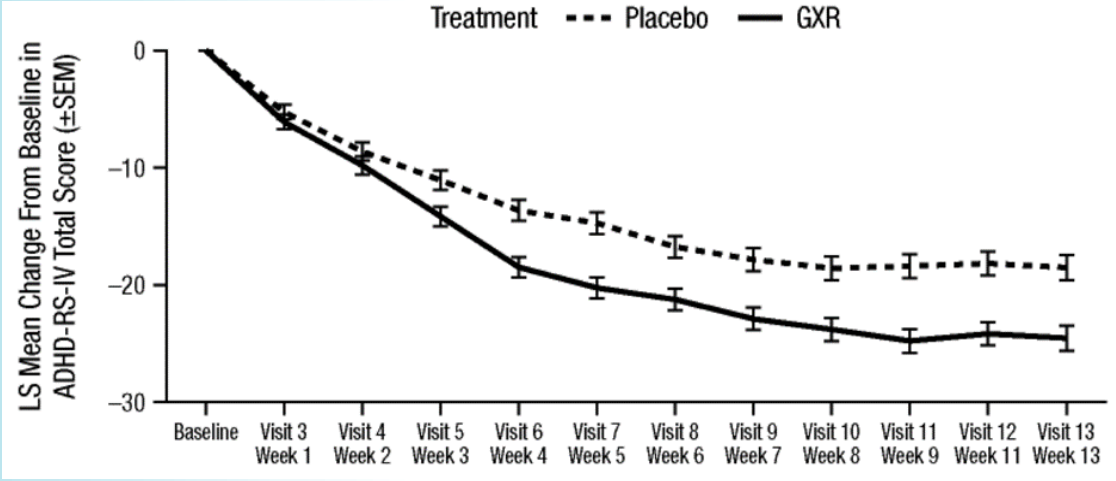
This 13-week, multicenter, randomized, double-blind, placebo-controlled trial evaluated once-daily GXR (1–7 mg per day) in adolescents with ADHD aged 13 to 17 years. The primary endpoint was the change from baseline in the ADHD Rating Scale–IV (ADHD-RS-IV) total score; key secondary endpoints included scores from the Clinical Global Impressions–Severity of Illness (CGI-S), and Learning and School domain and Family domain scores from the Weiss Functional Impairment Rating Scale–Parent Report (WFIRS-P) at week 13.

Results

A total of 314 participants were randomized (GXR, n = 157; placebo, n = 157). The majority of participants received optimal doses of 3, 4, 5, or 6 mg (30 [22.9%], 26 [19.8%], 27 [20.6%], or 24 [18.3%] participants, respectively), with 46.5% of participants receiving an optimal dose above the currently approved maximum dose limit of 4 mg. Participants receiving GXR showed improvement in ADHD-RS-IV total score compared with placebo (least-squares mean score change, –24.55 [GXR] versus –18.53 [placebo]; effect size, 0.52; $p < .001$). More participants on GXR also showed significant improvement in CGI-S scores compared with placebo (50.6% versus 36.1%; $p = .010$). There was no statistically significant difference between treatments at week 13 in the 2 WFIRS-P domains. Most treatment-emergent adverse events were mild to moderate, with sedation-related events reported most commonly.

Conclusion

GXR was associated with statistically significant improvements in ADHD symptoms in adolescents. GXR was well tolerated, with no new safety signals reported.



Wilens et al. *J Am Acad Child Adol Psych.* 2015;54:916-925.

Guanfacine Extended-Release in ADHD

(N=324 (51 sites); 6 weeks, mean age 11±3 yrs)

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- Adverse effects
  - Discontinuation rate similar: med vs placebo
  - Somnolence (27% vs 12%[placebo]) and fatigue (9% vs 3%)
    - Improved after titration
  - Headache (21% vs 11%)
- Cardiovascular changes (dose related)
  - Heart rate (-9.5 bpm at 4 mg [average change vs baseline])
    - 6-7% of subjects at 3-4 mg with HR<50
    - 1 subject with dizziness with standing (HR =64)
  - Systolic BP (-7.4 mmHg at 4 mg)
  - Diastolic BP (-5.4 mmHg at 4mg)

Sallee et al. J AM Acad Child Adolesc Psychiatry, 48:2, Feb 2009

Combination of Guanfacine XR plus Stimulants in the Treatment Of ADHD (N=455)

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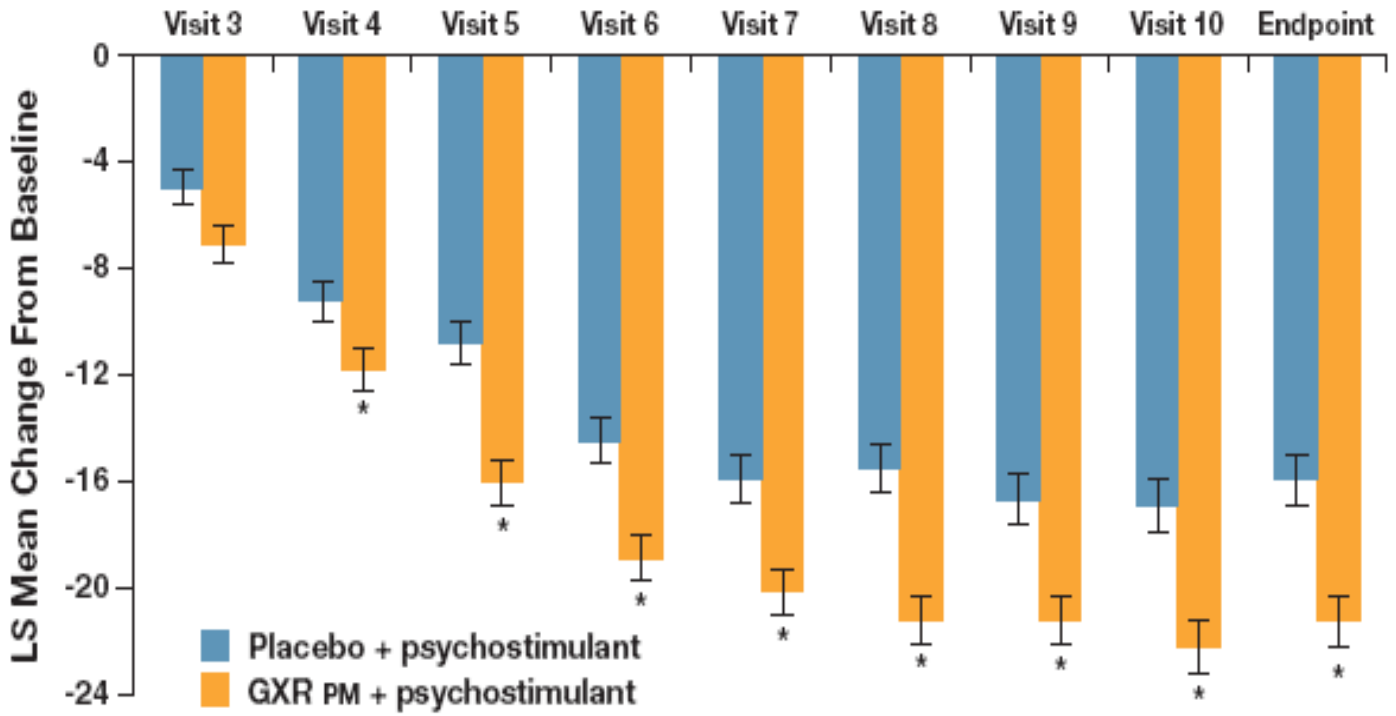
Figure 2. GXR PM dosing plus psychostimulant group: change in ADHD-RS-IV total score from baseline by visit (FAS).



*$P<0.05$ vs placebo, based on Dunnett's test.
Effect size at endpoint was 0.447.
Endpoint is the last valid assessment obtained after baseline and before dose taper.

Wilens et al. J Am Acad Child Adolesc Psych: 2012

Bupropion* in ADHD

- **Effective in children with ADHD**
  - **N=3 studies (104 subjects)**
- **Effective in adults with ADHD**
  - **N=5 controlled studies (including multisite)**
- **Response rate: 50-60%**
- **Effect size ca 0.5 (lower than stimulants)**
- **Use in ADHD plus mood/moodiness, cigarette smoking, adjunct with stimulants**
- **Demonstrated efficacy with in IR, SR, XL formulations**

***Not FDA approved for ADHD**
Wilens et al. *Biol Psych.* 2005.

Modafinil*: When to Use

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- **Effective in child but not adult studies (ADHD)**
- **Weak stimulant effects (Spencer et al.)**
- **Stimulant or nonstimulant non or partial responders (monotherapy, adjunctive therapy-no drug interactions with stimulants)**
- **Adverse effects to medications**
- **Concerns of diversion or misuse of stimulants**
- **Need for renewable agent**
- **Predominately cognitive deficits (e.g., motivation, arousal of attention)**
- **Stevens Johnson Syndrome Risk in peds; not approved for any Ped indication**
- **Cardiovascular risk factors (still cautionary in PI)**
- **Decreases blood levels of Oral Contraceptives**

***Not FDA approved for ADHD**
Wilens et al. *Biol Psych.* 2005.

Memantine* for Executive Dysfunction in Adults with ADHD

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Design

- **12 week RCT of adults with ADHD and Executive Function Deficits**
- **Dosing of up to 20 mg/day in 26 adults**
- **Adjunct to OROS – methylphenidate**

Findings

- **Trend improvements in executive functioning (by BRIEF; inhibition and self monitoring)**
- **No changes on automated neuropsychological functioning**
- **Adverse effects: Minor**
- **Other positive RCTs (European data)**

***Not FDA approved for ADHD**

Biederman et al. *J Atten Disorders*. 2017;21:4.

Summary: Non-Stimulant Pharmacotherapy of ADHD

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- **Non-stimulant medications and emerging neuro devices for ADHD**
- **Somewhat lower effect size than stimulants**
  - **However, 24 hour coverage; can be combined**
- **A variety of effective drugs**
  - **Noradrenergic agents (ATMX, VIL) – (FDA Approved Peds, Adol Adults)**
  - **Alpha agonists – FDA approved in Peds, used in adol and adults**
  - **Antidepressants/arousal agents – not FDA approved**
- **Often delayed onset-of-action for ADHD**
- **Useful in comorbidity**
- **FDA approval on co-administration with stimulants (alpha agonists)**
- **Multiple 'pipeline' nonstimulants and devices in development**