



# Pharmacotherapy of ADHD with Non-Stimulants

Timothy E. Wilens, M.D.

Chief, Division of Child and Adolescent Psychiatry,  
(Co)Director of Center for Addiction Medicine,  
Massachusetts General Hospital  
Massachusetts General Hospital for Children  
Professor of Psychiatry, Harvard Medical School



# Faculty Disclosure

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- Kempharm, Otsuka, NIH (NIDA), Ironshore, Vallon
- Licensing agreement with Ironshore (Before School Functioning Questionnaire)
- Clinical care: MGH, Bay Cove Human Services, Gavin/Phoenix, National Football League (ERM Associates), Major/Minor League Baseball
- (Co)Edited Straight Talk About Psychiatric Medications for Kids (Guilford); ADHD Across the Lifespan (Cambridge) , MGH Comprehensive Clinical Psychiatry (Elsevier), MGH Psychopharmacology and Neurotherapeutics (Elsevier)

Some of the medications discussed may not be FDA approved in the manner in which they are discussed including diagnosis(es), combinations, age groups, dosing, or in context to other disorders (e.g., substance use disorders)

# Pharmacotherapy for ADHD



- Stimulants (FDA Approved)

- Methylphenidate
- Amphetamine compounds

## Atomoxetine (FDA Approved)

## Alpha Agonists (FDA Approved [peds])

- Guanfacine (XR)
- Clonidine (XR)

## Combination Therapy (FDA Approved)

## Antidepressants

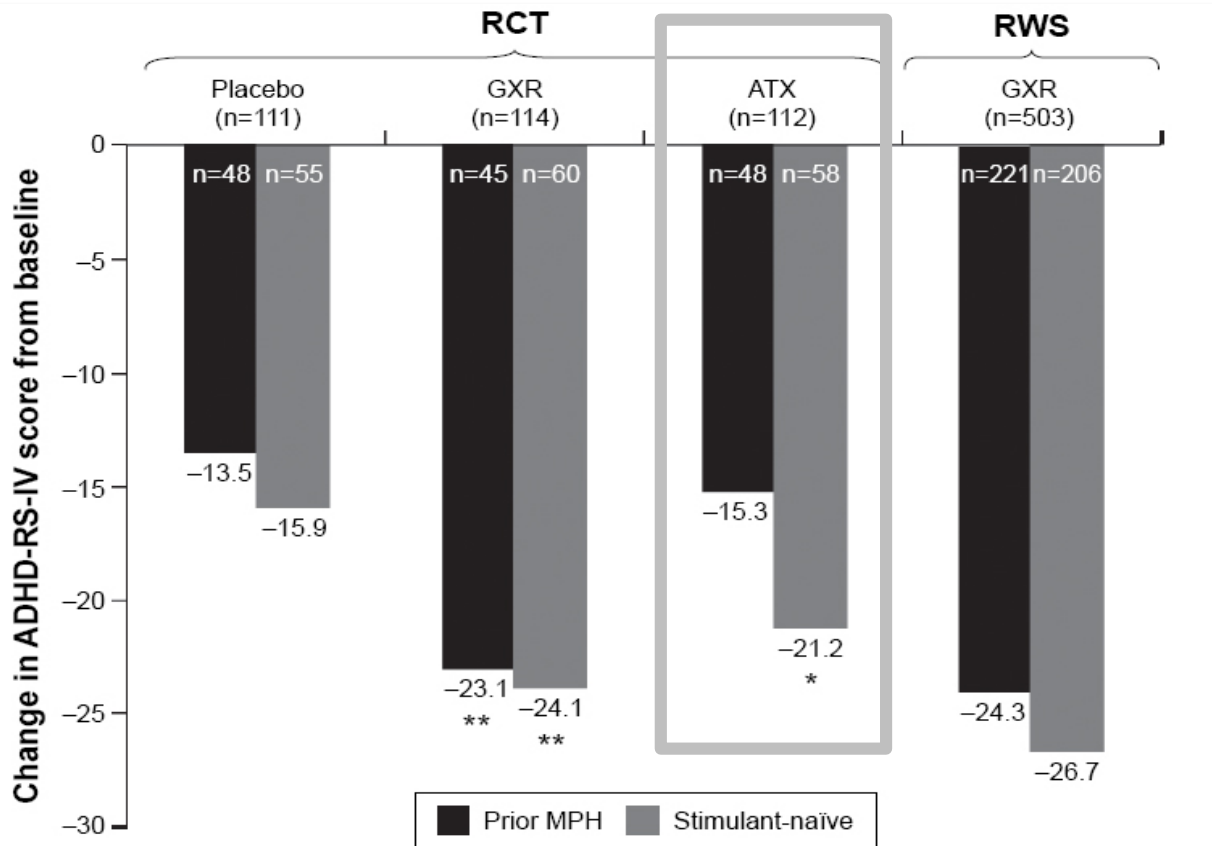
- Bupropion
- Tricyclics

## Modafinil

## Research

ADHD in Children & Adults. Adler, Spencer, Wilens (eds), Cambridge Press; 2015

# Previous Methylphenidate Exposure Influences Nonstimulant Outcomes



Mean change from baseline in ADHD-RS-IV total score by treatment for prior MPH or stimulant-naïve subgroups at endpoint (full-analysis set).

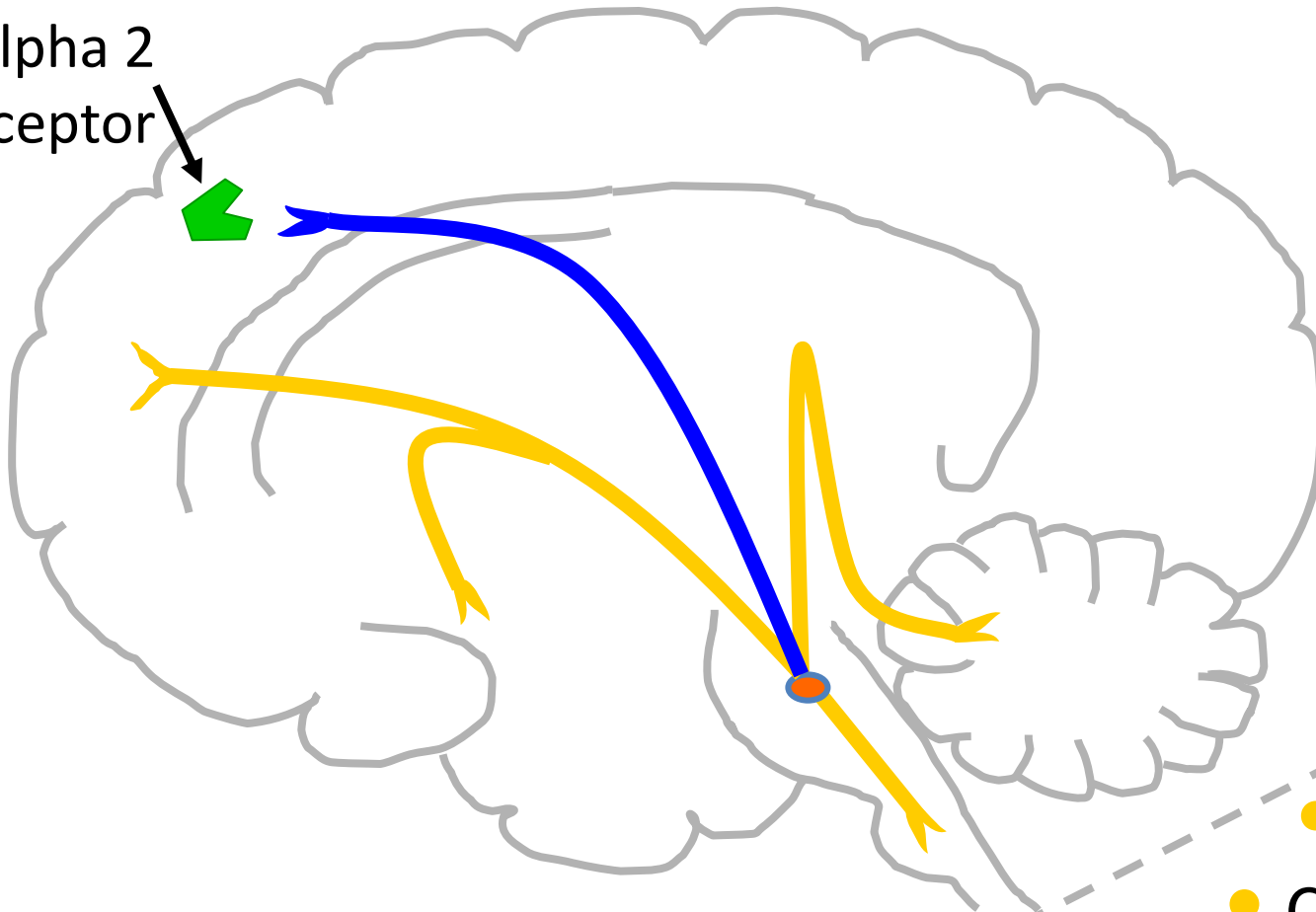
Notes: \*P<0.05, \*\*P<0.001 versus placebo. Nominal statistical differences based on ANCOVA of placebo-adjusted LS means in the RCT only. Statistics not performed for RWS. Not all patients had ADHD-RS-IV total score data available at endpoint.

Abbreviations: ADHD-RS-IV, ADHD Rating Scale version IV; ANCOVA, analysis of covariance; ATX, atomoxetine; GXR, guanfacine extended release; LOCF, last observation carried forward; LS, least squares; MPH methylphenidate; RCT, randomized controlled trial; RWS, randomized-withdrawal study.

Huss et al., *Neuropsychiatric Disease Tx*, 2016: 12; 1085-1101

# Norepinephrine Frontal

Alpha 2  
receptor

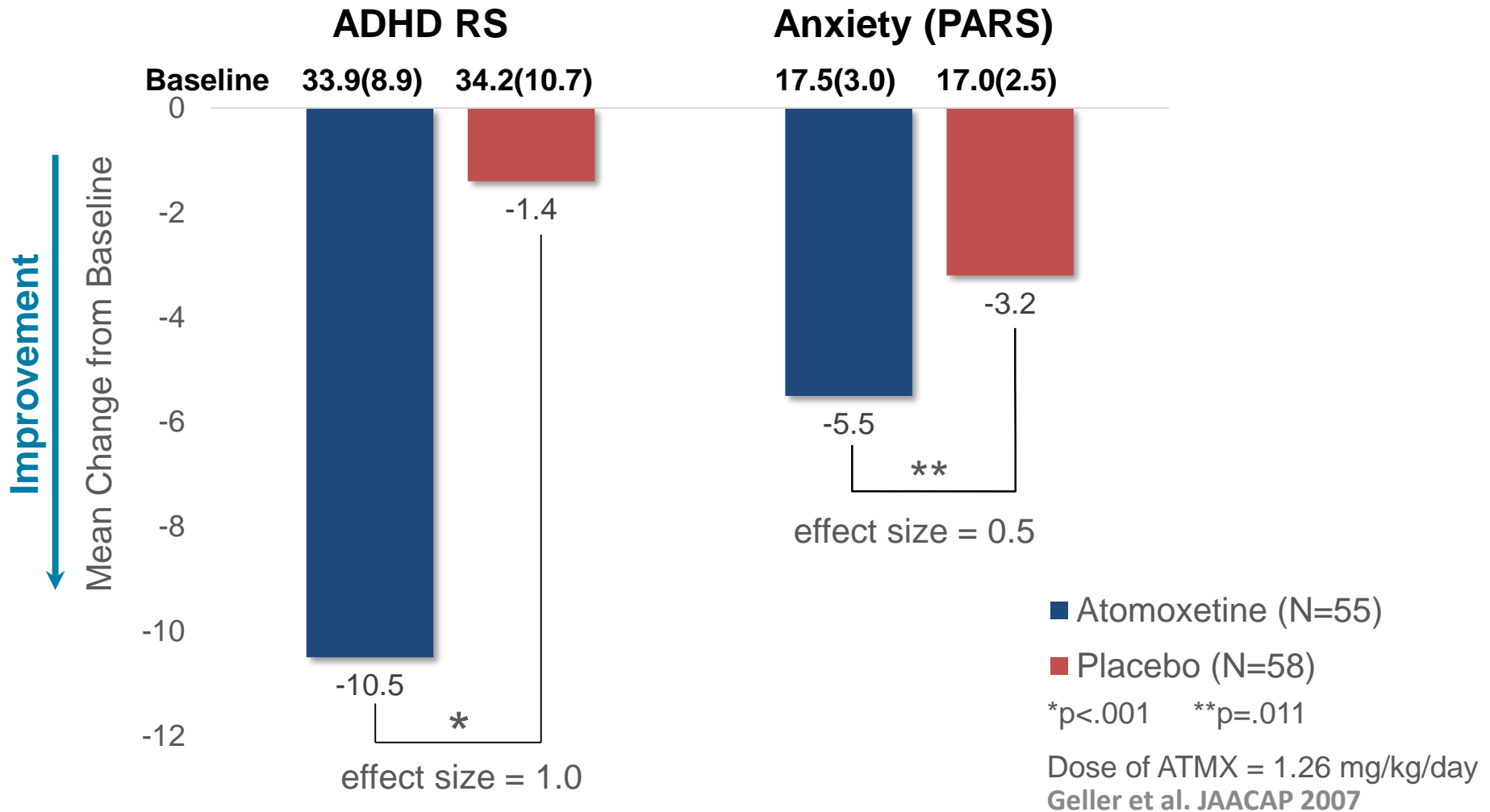


- Attention
- Concentration
- Other cognitive fxns

# Atomoxetine: When to Use

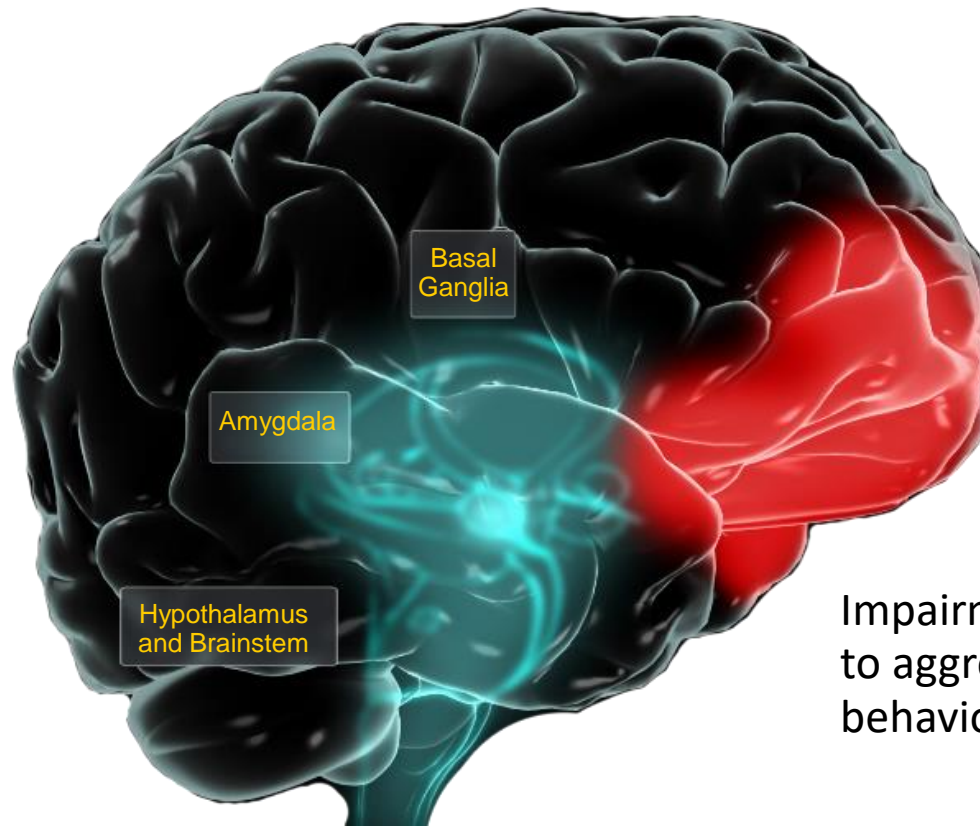
- Monotherapy (higher likelihood of response as first start)
- Stimulant nonresponders
- Stimulant partial responders (monotherapy, adjunctive therapy-no drug interactions with stimulants)
- Adverse effects to stimulants
- Concerns of stimulant diversion
- Executive dysfunction (?)
- Comorbid ADHD plus
  - Oppositional disorder
  - Anxiety
  - Tics
  - Substance abuse

# Atomoxetine Improves Anxiety and ADHD in Youth with ADHD & Anxiety



# The Ventromedial Prefrontal Cortex (PFC): Emotional Regulation

Ventromedial PFC is thought to regulate emotion<sup>1-3</sup>



Ventromedial  
PFC

Impairment may lead  
to aggressive and oppositional  
behavior

<sup>1</sup>Anderson SW, et al. *Nat Neurosci.* 1999;2:1032-1037.

<sup>2</sup>Arnsten AFT, et al. *J Child Adolesc Psychopharmacol.* 2007;17:393-406.

<sup>3</sup>Price JL, et al. *Prog Brain Res.* 1996;107:523-536.



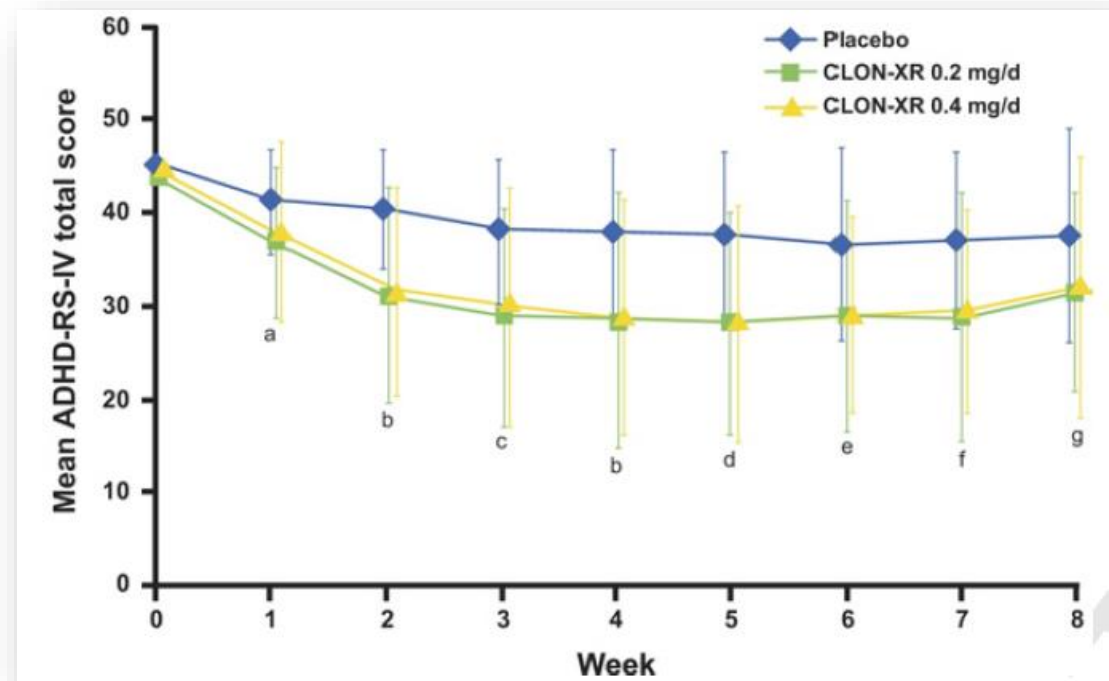
# Alpha Agonists: Clonidine & Guanfacine

- Alpha agonist agents
  - Mimics Norepinephrine at alpha and beta receptors
  - Presynaptic Alpha 2a (guanfacine more specific)
  - Post synaptic alpha 1, 2 a-c (alpha 2a in PFC)
- Effect on Prefrontal cortex (PFC)
  - May be dose dependent effects on pre/post 2a
  - Largely inhibitory
  - Modulated by “stress” dependent release of Nepi
  - Improves PFC blood flow and functioning in animal models
- Effect on Locus Coerulus
- Modulate of neurotransmission of other neuronal systems (glutamate, GABA, cholinergic, opioid)

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

# Extended Release Clonidine for ADHD

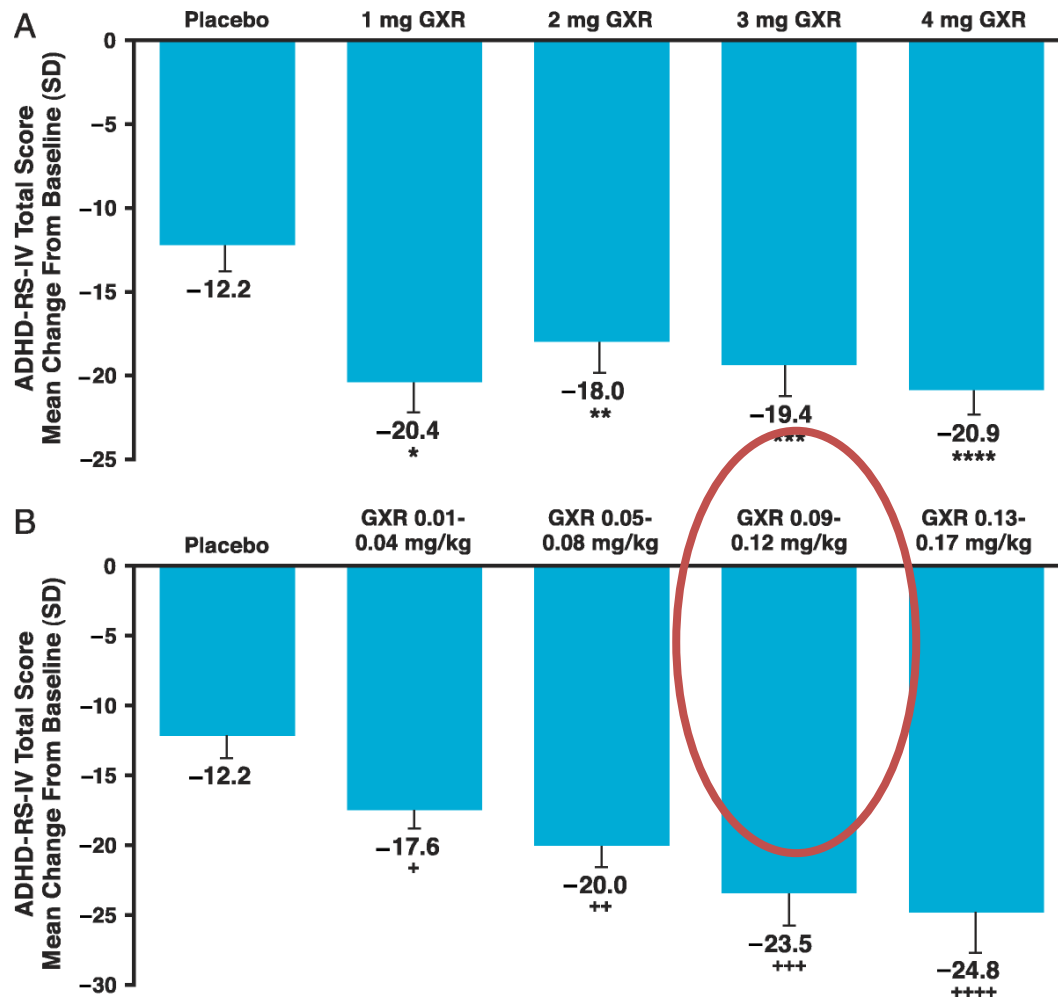
Mean ADHD Rating Scale—IV (ADHD-RS-IV) total score from baseline to Week 5, using a last observation carried forward (LOCF) method:



Note: ADHD-RS-IV total score was significantly improved at week 1 for the CLON-XR 0.2-mg/day group. Significant improvement was achieved in both CLON-XR groups beginning at week 2 and continued through study termination. Error bars represent standard deviations. CLON-XR= clonidine hydrochloride extended-release tablets; <sup>a</sup>  $p = .0219$  for CLON-XR 0.2 mg/day. <sup>b</sup>  $p < .0001$  for both groups. <sup>c</sup>  $p < .0003$  for both groups. <sup>d</sup>  $p = .0005$  for both groups. <sup>e</sup>  $p < .0054$  for both groups. <sup>f</sup>  $p < .0074$  for both groups. <sup>g</sup>  $p \leq .0288$  for both groups.

# Guanfacine Extended-Release in ADHD

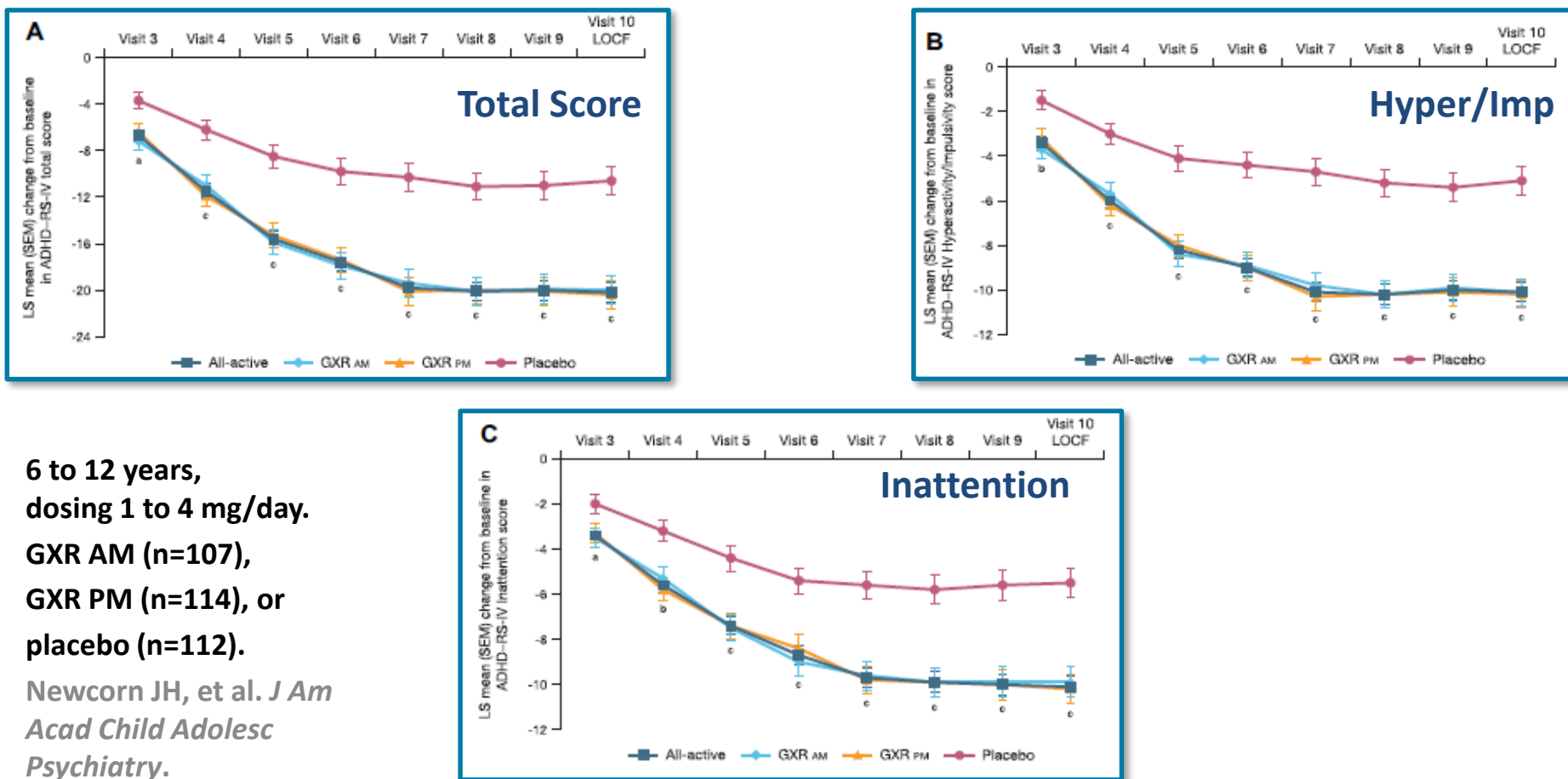
(N=324 [51 sites]; 6 weeks active\*, Mean Age 11±3 yrs)



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*, 48: 155-165; 2009

# Equal Efficacy with Guanfacine XR AM versus PM Administration



6 to 12 years,  
dosing 1 to 4 mg/day.

GXR AM (n=107),  
GXR PM (n=114), or  
placebo (n=112).

Newcorn JH, et al. *J Am Acad Child Adolesc Psychiatry*.

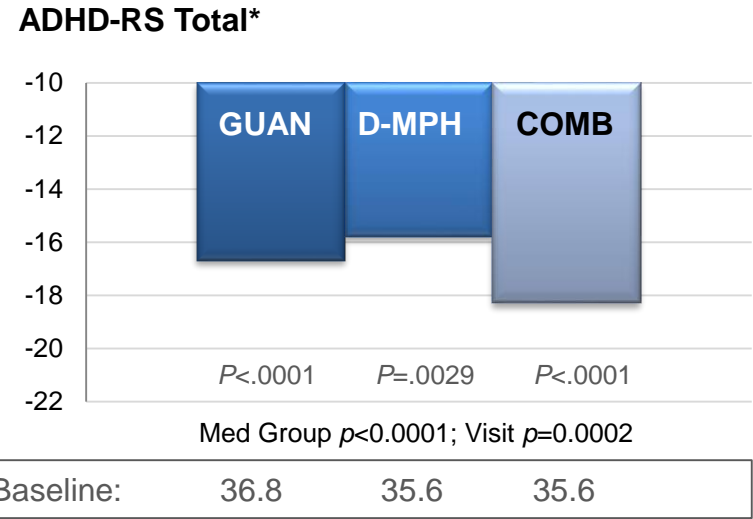
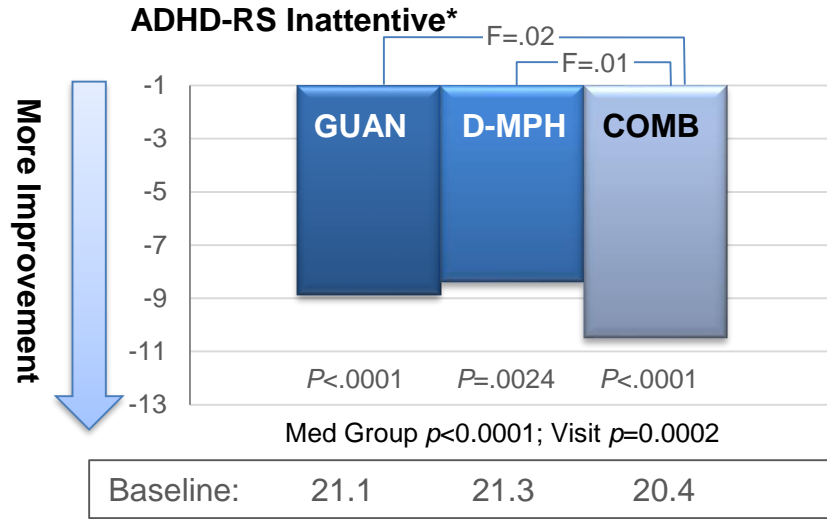
2013;52(9):921-930.

**FIGURE 2** Mean change from baseline in attention-deficit/hyperactivity disorder (ADHD) Rating Scale-IV (ADHD-RS-IV) scores by visit. Note: (A) Total score. (B) Hyperactivity/Impulsivity subscale. (C) Inattention subscale. All  $p$  values are based on type III sum of squares from an analysis of covariance (ANCOVA) model. GXR = guanfacine extended release; LOCF = last observation carried forward; LS = least squares; SEM = standard error of the mean. <sup>a</sup> $p < .05$  versus placebo based on change from baseline (visit 2). <sup>b</sup> $p < .01$  versus placebo based on change from baseline (visit 2). <sup>c</sup> $p < .001$  versus placebo based on change from baseline (visit 2).

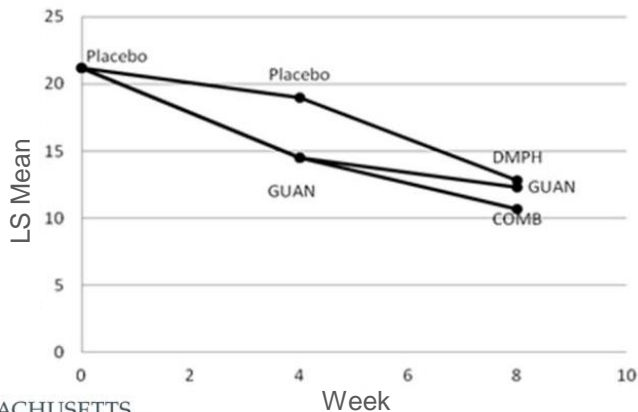
# Alpha Agonists: When to Use

- Monotherapy
- Stimulant or nonstimulant nonresponders
- Medication partial responders (adjunctive therapy)
  - Studied with stimulant coadministration (N=5 studies)
- Adverse effects to stimulants or nonstimulants
- Comorbid ADHD plus
  - Oppositional disorder
  - Anxiety
  - Tics
  - “Emotional dysregulation” (needs to be studied)
- Potentially younger children (needs to be studied)

# RCT on Guanfacine (GUAN), D-Methylphenidate (D-MPH), or the Combination (COMB) on ADHD in Children



**ADHD-RS-IV Inattention Subscale  
LS Means for Current Treatment By Time**



\*Denotes least squares mean end point changes in ADHD Rating Scale Score versus baseline

**8-week RCT, 3-arm trial in 207 participants**

**Age:** 7 – 14 years

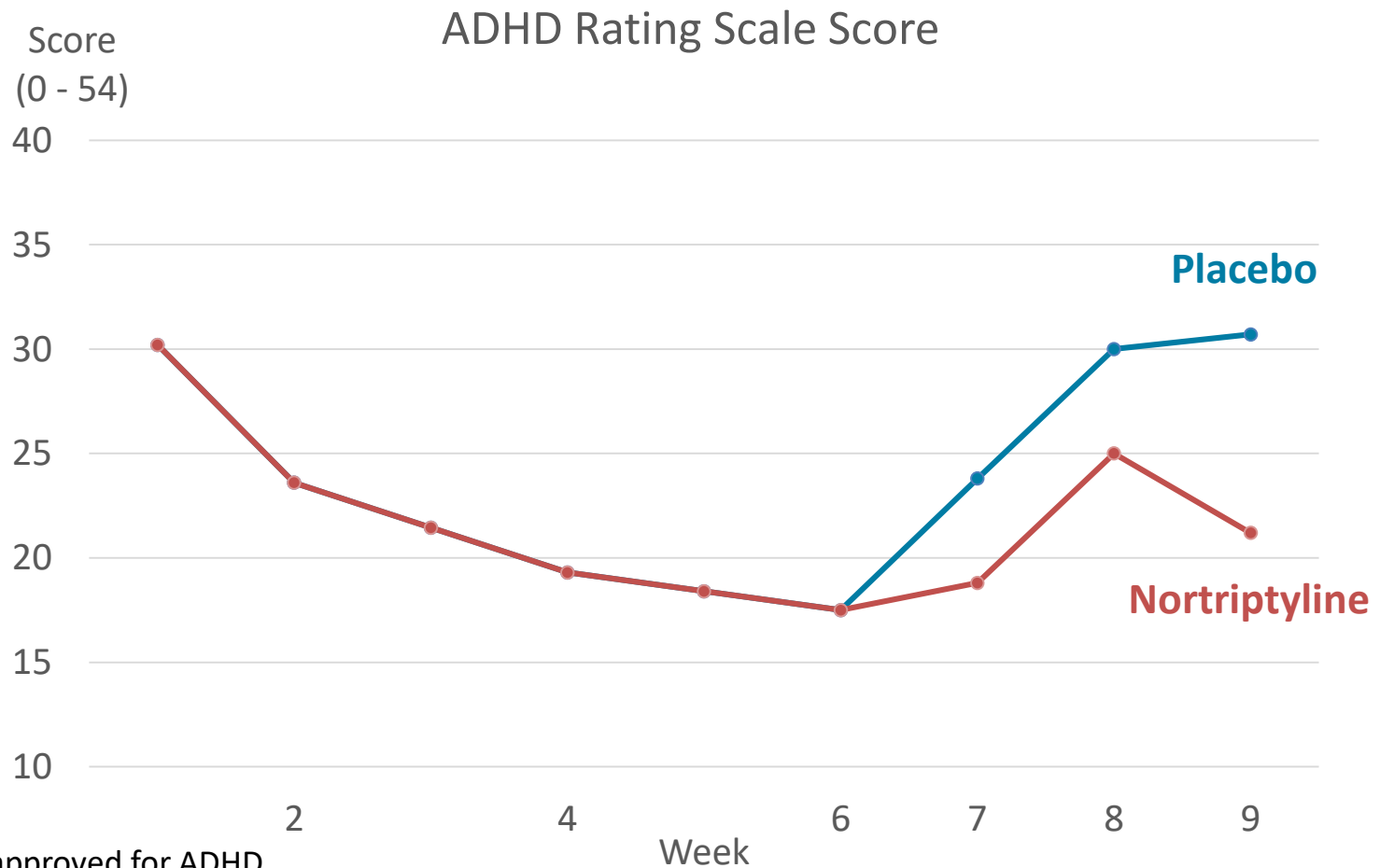
**Sample Size:** GUAN (n=68), D-MPH (n=69), COMB (n=70)

**Dosing:** GUAN (1-3 mg/day), D-MPH (5-20 mg/day)

# Bupropion

- Effective in children with ADHD
  - N= 3 studies (104 subjects)
- Effective in adults with ADHD
  - N= 5 controlled studies (including multisite)
- Effect size ca 0.5 (lower than stimulants)
- Use in ADHD plus mood, cigarette smoking, adjunct with stimulants

# Nortriptyline\* in Pediatric ADHD



\*Not FDA approved for ADHD

Prince, et al., J Child Adolesc Psychopharm, 2000



# Modafinil\*: When to Use

- 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
- Cardiovascular risk factors (still cautionary in PI)
- Predominately cognitive deficits (e.g., motivation, arousal of attention)

\*Not FDA approved for ADHD

# Combination of Atomoxetine plus Stimulants\* in the Treatment Of ADHD

- Qualitative analysis of existing studies
- N=3 prospective (1RCT)+ 7 retrospective reports
- Predominately children/adolescent with inadequate response to stimulants
- Most often used stimulant = methylphenidate
- Conclusions
  - Small sample sizes
  - *“Existing evidence suggests, but does not confirm, that this drug combination may benefit some, but not all, patients who have tried several ADHD medications without success”*

Truer et. al. J Child Adolesc Psychopharmacol. 2013 Apr; 23(3): 179–193

# Viloxazine\* for ADHD

**Agent: Serotonergic and noradrenergic**

**Study: Phase II in 6-12 yo children with ADHD**

**N= 222 children (placebo**

**8 week phase II study of 100, 200, 300, 400 mg**

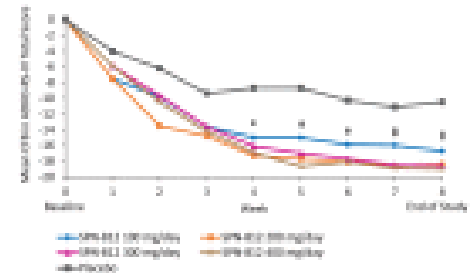
**Findings:**

**Significant effects at all doses**

**Effect sizes of 0.55, 0.6, 0.62, respectively**

**Side effects;**

**Somnolence, headache, decreased appetite**



(Johnson et al., J Att Disorder, 2020: 24(2):348-358)

# Molindone\* for Impulsive/Aggressive ADHD

## Agent

- Extended-release antipsychotic (traditional)

## Design

- Study of 121 children with ADHD with persistent impulsive/aggression
- Phase II RCT of low (<18 mg), medium (<36 mg), & higher dosing (<54 mg) PLUS existing pharmacotherapy (stimulant/nonstimulant)

## Findings

- Improved Modified Overt Aggression Scale scores
- Adverse effects: Headaches, sedation, increased appetite

\*Not FDA approved for ADHD

# Summary: Non-Stimulant Pharmacotherapy of ADHD

- A number of non-stimulant medications for ADHD
- Often somewhat lower effect size than stimulants
- FDA approved in combination with alpha agonists
- Response may be related to previous stimulant exposure
- A variety of effective drugs
  - Noradrenergic agents (ATMX) -(FDA Approved)
  - Alpha agonists - FDA approved
  - Antidepressants /arousal agents -second line
- Often delayed onset-of-action for ADHD
- Useful in comorbidity
- New nonstimulants in development