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

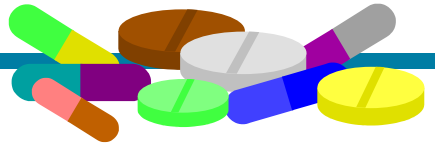
Faculty Disclosure

Timothy Wilens, M.D. has served as a consultant, or has received grant support from the following:

- 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

Atomoxetine

- FDA approval across the lifespan
- Efficacy as monotherapy (higher likelihood of response as first start)
- Less responsivity in stimulant nonresponders
- Effectiveness data in stimulant partial responders (adjunctive therapy-no drug interactions with stimulants)
- No concerns of stimulant diversion
- May be helpful in cognitive executive dysfunction (?)
- Comorbid ADHD plus
  - Oppositional disorder
  - Anxiety
  - Tics
  - Substance use disorders

Atomoxetine in Adults with ADHD and Social Anxiety Disorder

Design

- Double blind, placebo controlled study
- Adults with DSM IV ADHD and Social Anxiety Disorder (SAD)
- Dosing of atomoxetine of up to 100 mg/day
- 2 week placebo washout followed by 14 week trial

Results (versus placebo)

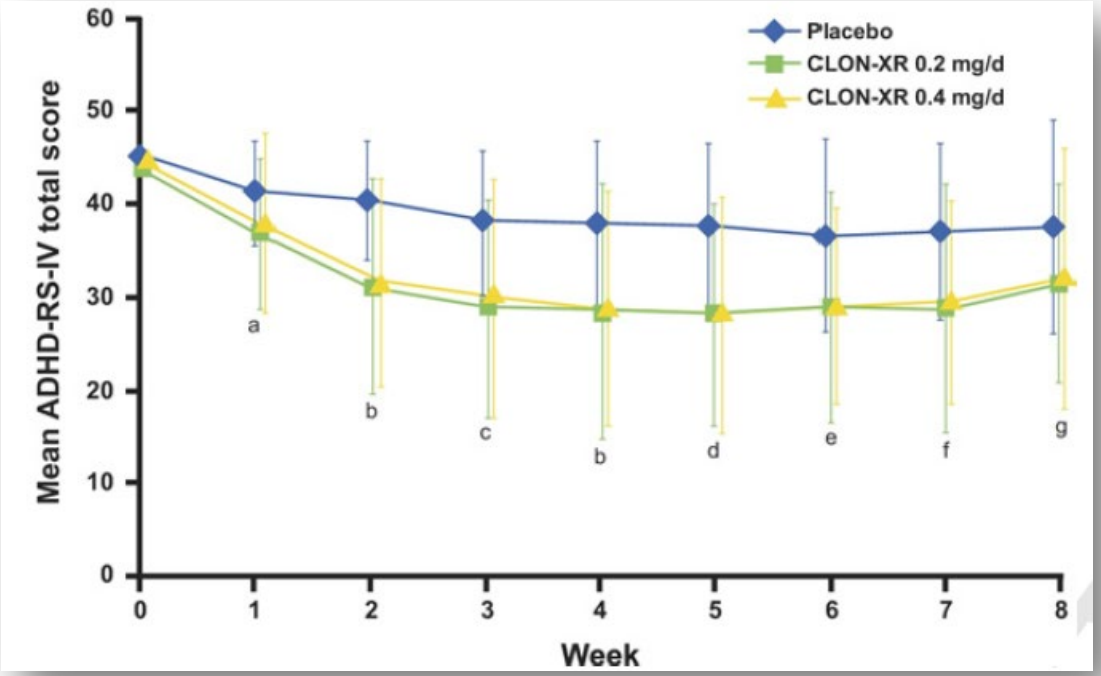
- Significant effect on ADHD (2 scales)
- Significant effect on Anxiety (3 scales)
- Week to week improvement
- Side effects: predictable ATX effects

Conclusions: Atomoxetine effective for ADHD and Social Anxiety Disorder in adults

Adler et al, *Depress Anxiety*. 2009;26(3):212-21

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; [a] $p = .0219$ for CLON-XR 0.2 mg/day. [b] $p < .0001$ for both groups. [c] $p < .0003$ for both groups. [d] $p = .0005$ for both groups. [e] $p < .0054$ for both groups. [f] $p < .0074$ for both groups. [g] $p \leq .0288$ for both groups.

N=236; 61% completion rate

Jain et al. JAACAP epub 2011

Guanfacine XR in Adolescent ADHD

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

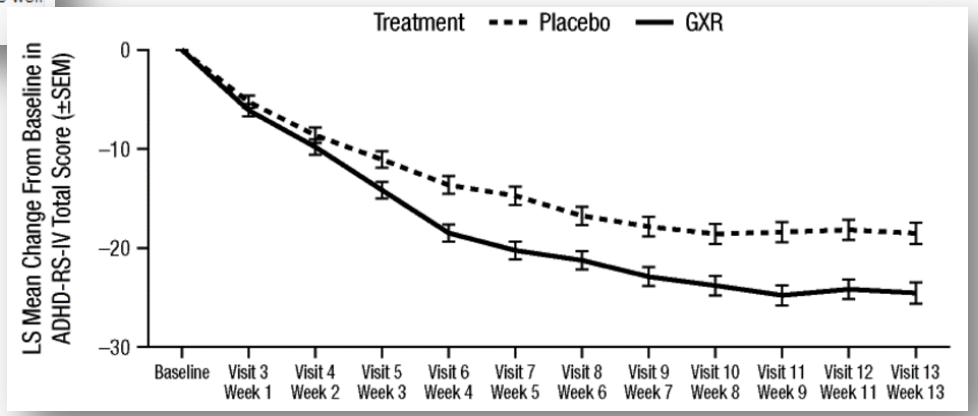
This 13-week, multicenter, randomized, double-blind, placebo-controlled trial evaluated once-daily GXR (1–7 mg per day) in adolescents with ADHD aged 13 to 17 years. The primary endpoint was the change from baseline in the ADHD Rating Scale–IV (ADHD-RS-IV) total score; key secondary endpoints included 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 XR in Adults with ADHD (Shorter term RCT)

Design

Phase III placebo controlled study of guanfacine in 201 adults with ADHD

- Dosing 2-6 mg/day
- 5 week dose titration, 5 weeks maintenance
- No serious AEs

Findings

- GXR > Placebo (Effect size of 0.57)
- Responder (by CGI): 48% vs 22%
- Improved inattention, hyp/imp subscales

Adverse effects

-Discontinuation rate (20% vs 3%)
- Sedation, dry mouth, reduced BP most common
- HR (-10 bpm) and BP (- 7 to 10 mm/Hg) with GXR

Iwanami et al. J Clin Psychiatry 2020;81(3):19m12979

Guanfacine XR in Adults with ADHD (50 week open study)

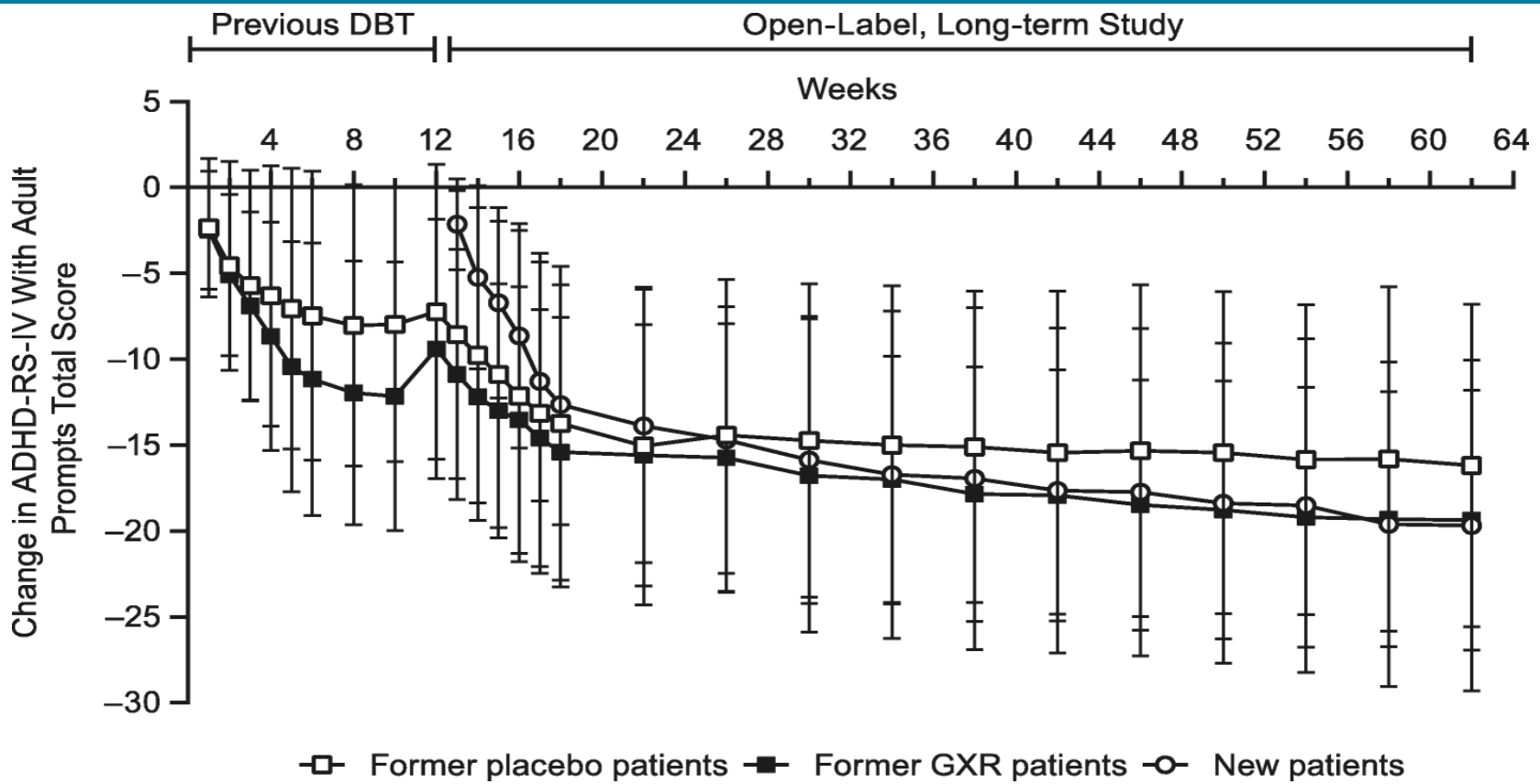
Design
Open followup of controlled clinical trial
Duration of up to 50 weeks
N= 150 from RCT; 41 newly enrolled
Maintenance dose of 4-6 mg/day

Findings
- Improved ADHD RS IV (ADHD symptoms) throughout study
- Most response in first 6 weeks; no tolerance

Adverse effects
-Discontinuation rate (20%; majority discontinued with cardiovascular concerns)
- Sedation, dry mouth, reduced BP/HR most common
- 2 serious AEs

Iwanami et al. B*MC Psychiatry* **volume 20**, Article number: 485 (2020)

Guanfacine XR in Adults with ADHD



Change from baseline in ADHD-RS-IV total scores. Data are the mean change from baseline (i.e., the start of the previous double-blind trial [DBT]) for patients who transitioned from the placebo arm and guanfacine extended-release (GXR) arm and the mean change from week 0 of the long-term treatment study for new patients. Error bars denote standard deviations.

Iwanami et al. B*MC Psychiatry* **Vol 20**: 485 (2020)

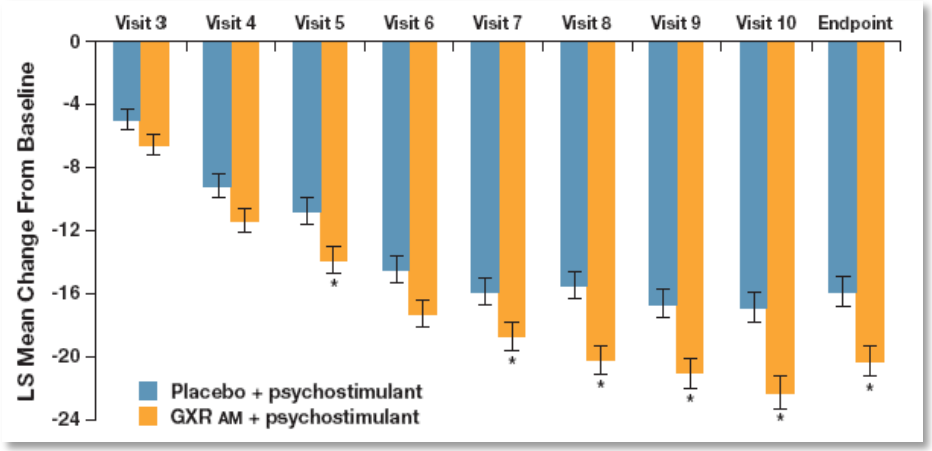
Alpha Agonists: When to Use

- 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)
  - Substance use disorders (needs to be studied)
- Potentially younger children (needs to be studied)

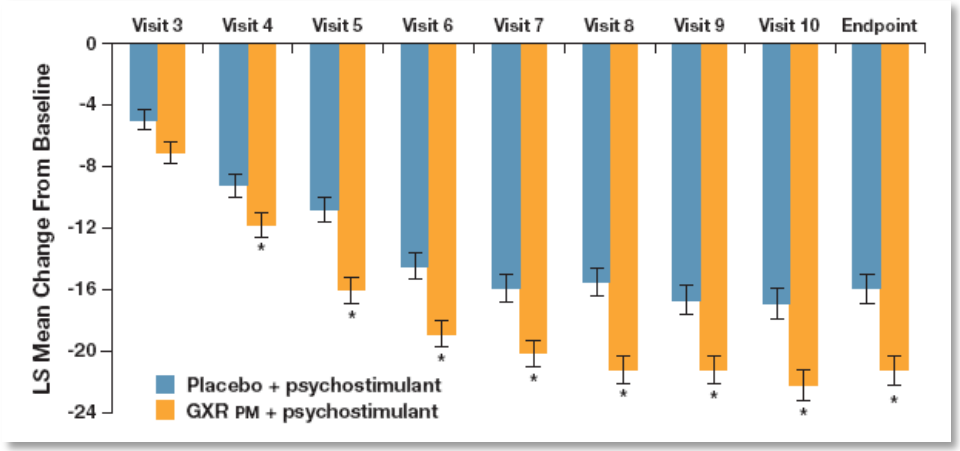
Combination of Guanfacine XR + Stimulants in the Treatment of ADHD (N=455)

Change in ADHD-RS-IV Total Score from Baseline by Visit (FAS)

GXR AM Dosing Plus Psychostimulant Group



GXR PM Dosing Plus Psychostimulant Group



*P<05 vs placebo, based on Dunnett's test. Effect size at endpoint was .377 for AM group, .447 for PM group. Endpoint is the last valid assessment obtained after baseline and before dose taper. FAS = full analysis set.

Wilens TE, et al. *J Am Acad Child Adolesc Psychiatry*. 2012;51(1):74-85.e2.

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

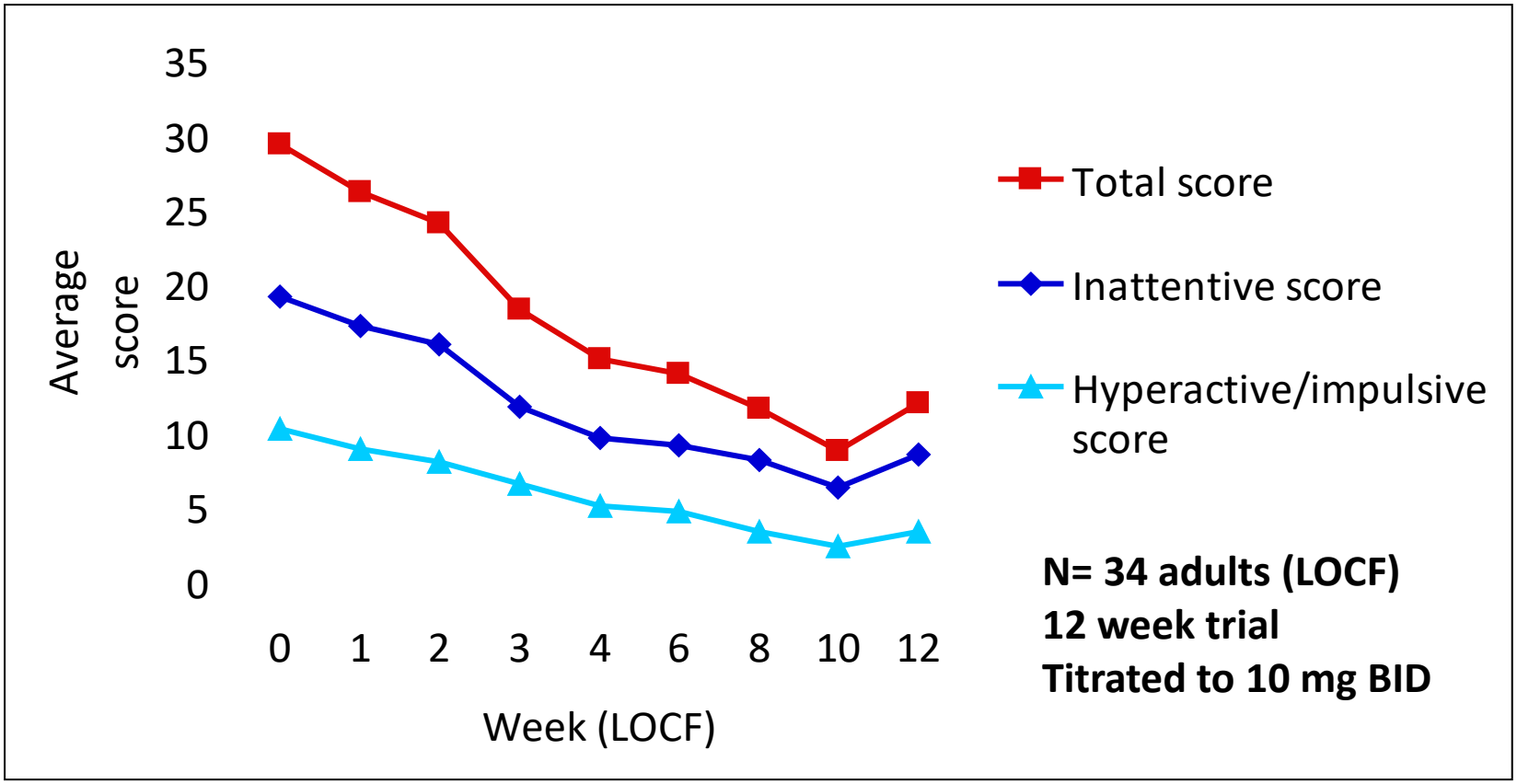
Tricyclic Antidepressants in ADHD

- Effective in children with ADHD
  - Use as monotherapy and adjunctly
  - Trials predominately of imipramine, desipramine, nortriptyline
  - Use in ADHD, ADHD plus tics/TS
- Effective in adults with ADHD
  - Use as monotherapy
  - Studies largely with desipramine
- Effect size ca 0.7-0.8 (est)-< Stimulants
- Need to monitor serum level, ECG (?), side effects, OD risk

Modafinil: When to Use

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

Memantine* for ADHD: Open Trial in ADHD Symptoms (AISRS Total)



Surman et al. World J Biol Psychiatry. 2013 May;14(4):291-8.

*Not FDA approved for ADHD

Memantine* for Executive Dysfunction in Adults with ADHD

Design

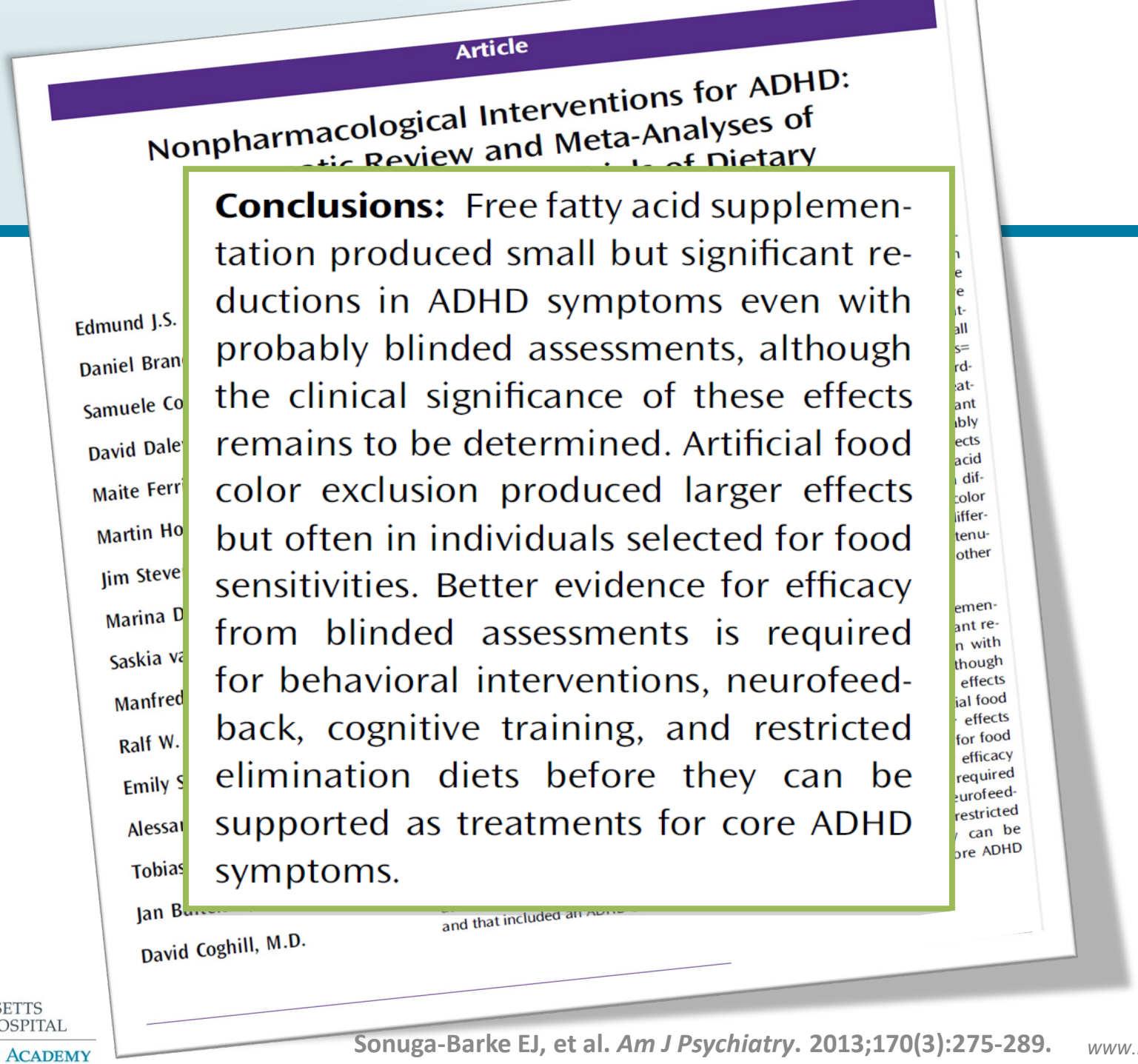
- **12 week RCT of adults with ADHD and Executive Function Deficits**
- **Dosing of up to 20 mg/day in 26 adults**
- **Adjunct to OROS - methylphenidate**

Findings:

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

(Biederman et al., J Atten Disorders, 2017: 21:4:)

*Not FDA approved for ADHD



Sonuga-Barke EJ, et al. *Am J Psychiatry*. 2013;170(3):275-289.

Omega -3/Omega-6 Fatty Acids* for ADHD

- Metanalysis of 10 studies (N= 699 children)
  - Examined EPA, DHA (Omega-3), and g-linoleic acid (Omega 6)
  - Indicating mild improvement in ADHD overall with good tolerability (ES = 0.28 monotherapy; 0.18 adjunct)
  - Potential dose response effect of EPA (omega 3)
  - Useful adjunctly for mood symptoms in treated ADHD
- Dosing
  - High EPA to DHA (docohexaenoic acid) or g-linoleic acid (omega 6)
  - 1000 mg/day (child); 2000 mg/day (adults)
  - Preparations, brands vary dramatically

Wilens et al, JCAP, 2017; Bloch MH, Qawasmi A, J Am Acad Child Adoles Psych 2011
Wozniak et al. Eur Neuropsychopharmacol. 2007 Jan 25 (epub)

*Not FDA approved for ADHD

Viloxazine* for ADHD

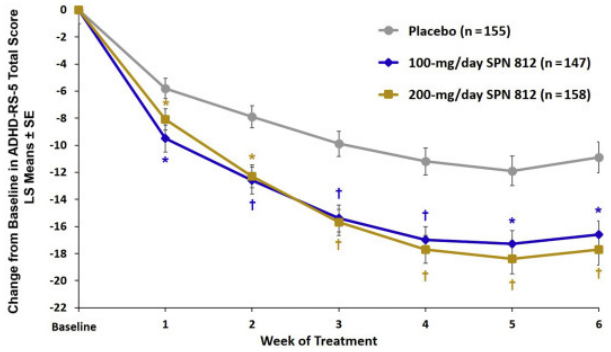
- **Noradrenergic & Serotonergic reuptake inhibitor**
- **Phase III, 6 week RCT study**
- **N = 444 children with ADHD**

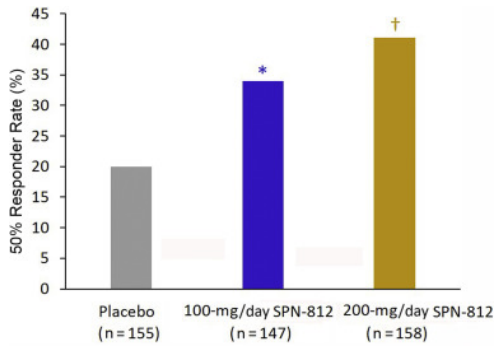
Findings

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

Side effects

- **Somnolence, decreased appetite, headache**

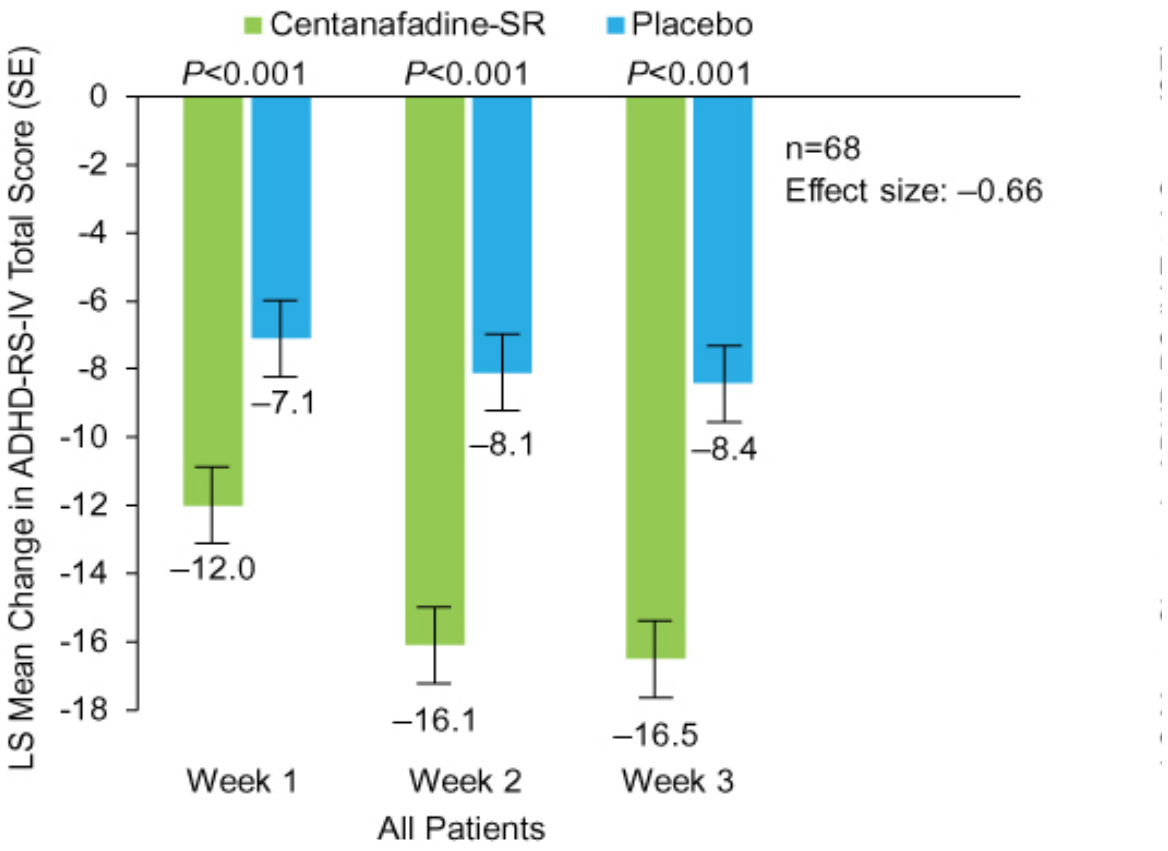




(Nasser et al, Clin Ther 2020:x 42(8):1452-1466)

*Not FDA approved

Centanafadine SR* for Adult ADHD (Triamine reuptake blocker)



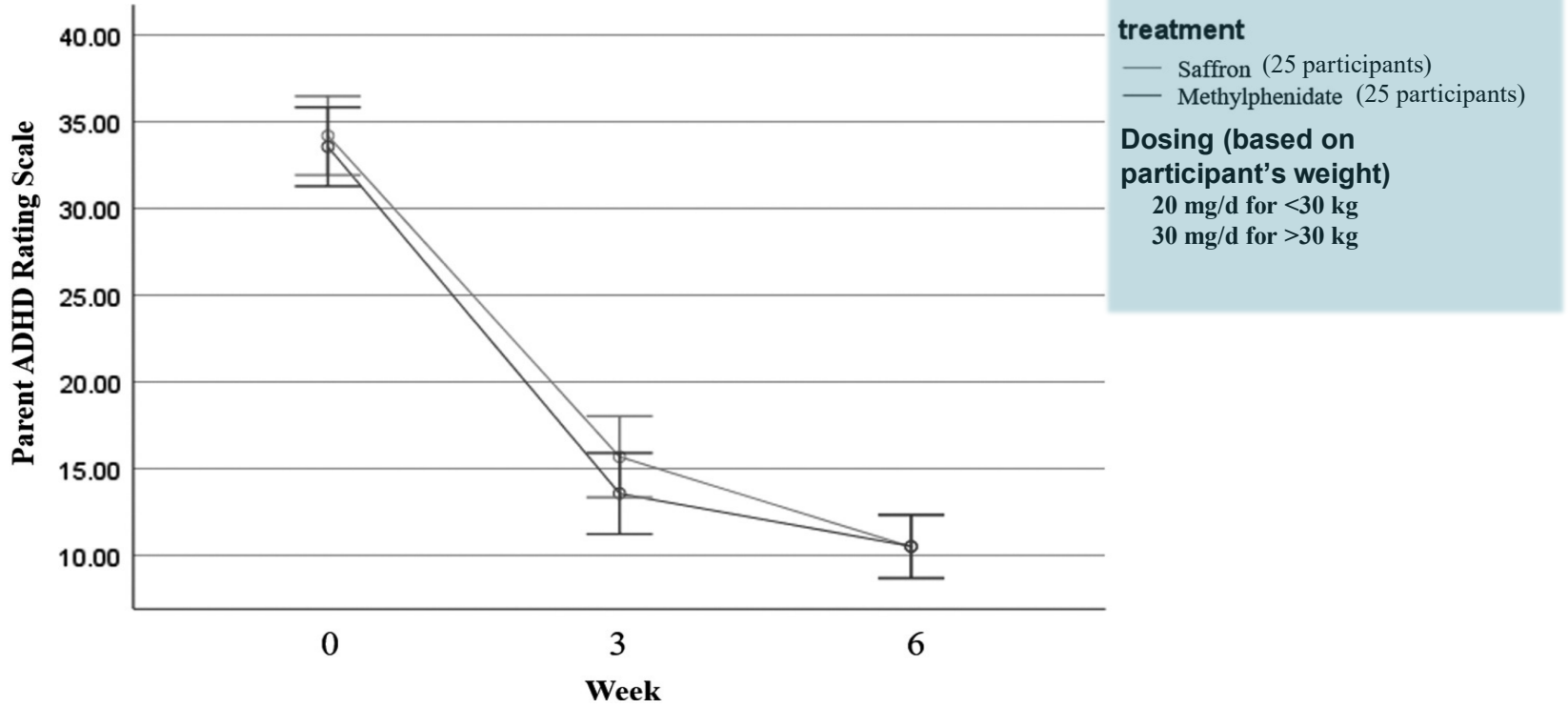
*Not FDA approved

Wigal SB, Wigal T, Hobart M, Madera JJ, Baker RA, Kohegyi E, McKinney A, Wilens TE. Safety and Efficacy of Centanafadine Sustained-Release in Adults With ADHD: Results of Phase 2 Studies. *Neuropsychiatr Dis Treat*. 2020;16:1411-1426

RCT with Saffron* Showed Similar Efficacy to Methylphenidate

Repeated measure for comparison of the effects of two treatments on Parent ADHD Rating Scale score* (pNS)

- Values represent mean ± standard error of mean



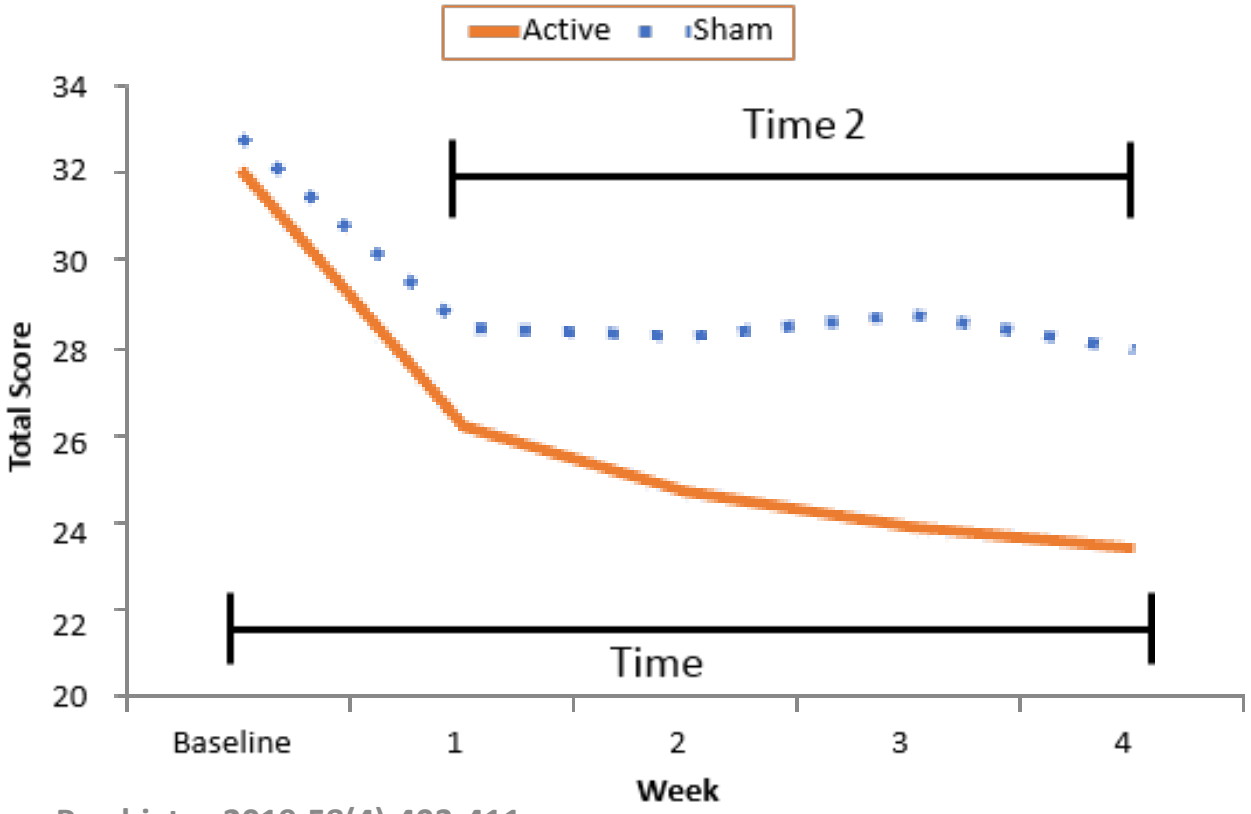
*Parent ADHD Rating Scale Version IV

Baziar and Aqamolaei, et al. *J Child Adolesc Psychopharmacol.* 2019;29(3):205-212

*Not FDA approved for ADHD

Trigeminal Nerve Stimulation for ADHD

ADHD RS Over 4-week Trial
Active (N=32) Versus Sham (N=30) Trigeminal Nerve Stimulation



McGough et al. J Am Acad Adolesc Psychiatry 2019;58(4):403-411

FDA NEWS RELEASE

FDA Permits Marketing of First Game-Based Digital Therapeutic to Improve Attention Function in Children with ADHD

Share Tweet Linkedin Email Print

Fc June 15, 2020

Español

Today, the U.S. Food and Drug Administration (FDA) permitted marketing of the first game-based digital therapeutic device to improve attention function in children with attention deficit hyperactivity disorder (ADHD). The prescription-only game-based device, called EndeavorRx, is indicated for pediatric patients ages 8 to12 years old with primarily inattentive or combined-type ADHD who have demonstrated an attention issue. EndeavorRx is indicated to improve attention function as measured by computer-based testing and is the first digital therapeutic intended to improve symptoms associated with ADHD, as well as the first game-based therapeutic granted marketing authorization by the FDA for any type of condition. The device is intended for use as part of a therapeutic program that may include clinician-directed therapy, medication, and/or educational programs, which further address symptoms of the disorder.

FDA Press Release Accessed *at https://www.fda.gov/news-events/press-announcements/fda-permits-marketing-first-game-based-digital-therapeutic-improve-attention-function-children-adhd*

Summary: Non-Stimulant Pharmacotherapy of ADHD

- A number of non-stimulant medications for ADHD
- Often somewhat lower effect size than stimulants
- A variety of effective drugs
  - Noradrenergic agents (ATMX) -(FDA Approved)
  - Alpha agonists - FDA approved, used in adol and adults
  - Antidepressants /arousal agents -second line
- Often delayed onset-of-action for ADHD
- Useful in comorbidity
- FDA approval on co-administration with stimulants
- Multiple 'pipeline' nonstimulants in development