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Pharmacotherapy of ADHD with Non-Stimulants

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Faculty Disclosure

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- NIH (NIDA), Food and Drug Administration, 3D Therapy
- Licensing agreement with Ironshore (Before School Functioning Questionnaire)
- Clinical care: MGH, Bay Cove Human Services, Gavin, 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), Update on Pharmacotherapy of ADHD (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

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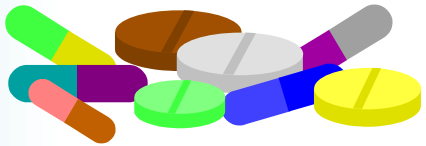
- Stimulants (FDA Approved)
  - Methylphenidate
  - Amphetamine compounds
- Atomoxetine (FDA Approved)
- Viloxazine XR (FDA Approved)
- Alpha Agonists (FDA Approved [Peds])
  - Guanfacine (XR)
  - Clonidine (XR)
- Combination Therapy (FDA Approved [Peds])
- Antidepressants
  - Bupropion
  - Tricyclics
- Modafinil
- Memantine
- Research



ADHD in Children & Adults. Adler, Spencer, Wilens (eds). Cambridge Press; 2015.
Newcorn & Wilens (eds). Update in Pharmacotherapy of ADHD. *Child Adolesc Psych Clin N America*. 2022 (in press).

Viloxazine XR for ADHD

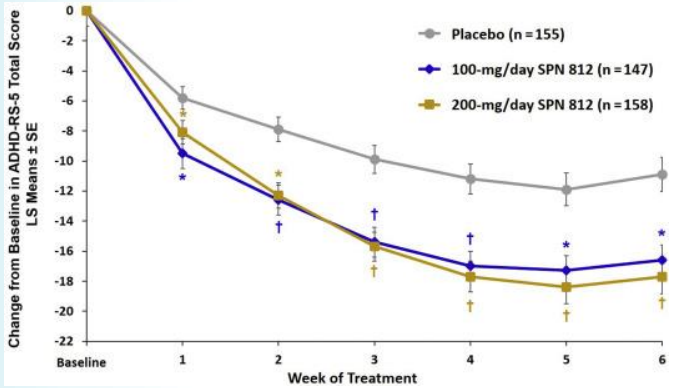
- Noradrenergic reuptake inhibitor
- Approved in children, adolescents, and adults
- Phase III, 6 week RCT study
- N = 444 children with ADHD
- [Positive trials in adolescents and adults]

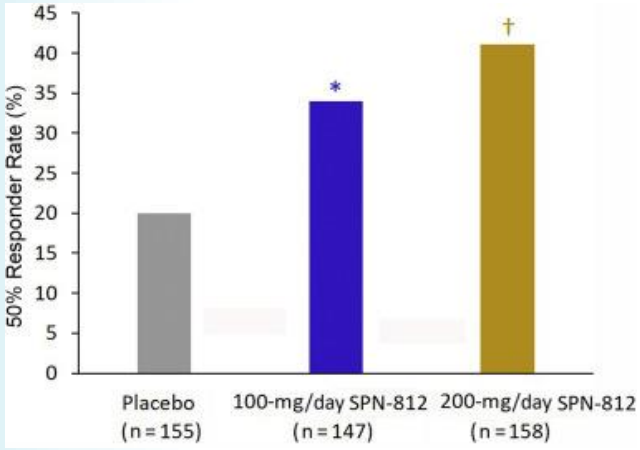
Findings

- 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

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- **Package Insert:**
  - **Dosing of 100 – 400 mg daily**
  - **Children: start with 100 mg x 1 week, then increase to 200 mg/day**
  - **Adolescents: Start with 200 mg x 1 week, then increase to 400 mg/day**
  - **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, which may increase the risk of adverse reactions associated with these CYP1A2substrates.**
- **Coadministration with viloxazine XR is contraindicated. Examples Alosetron, duloxetine, ramelteon, tizanidine, theophylline**
- **Careful with caffeine**
- **Unclear effect on melatonin**

Viloxazine XR: Potential Uses

- Monotherapy for ADHD
- Treatment non-response/intolerance to stimulants, nonstimulants
- Patients with high risk for substance misuse, or with substance use disorders
- Comorbid ADHD
  - European approval of IR formulation and use for depressive disorders (pulled from market)
  - Executive dysfunction?
  - Autistic traits?
  - Stay tuned for more signals

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

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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

Conclusion

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

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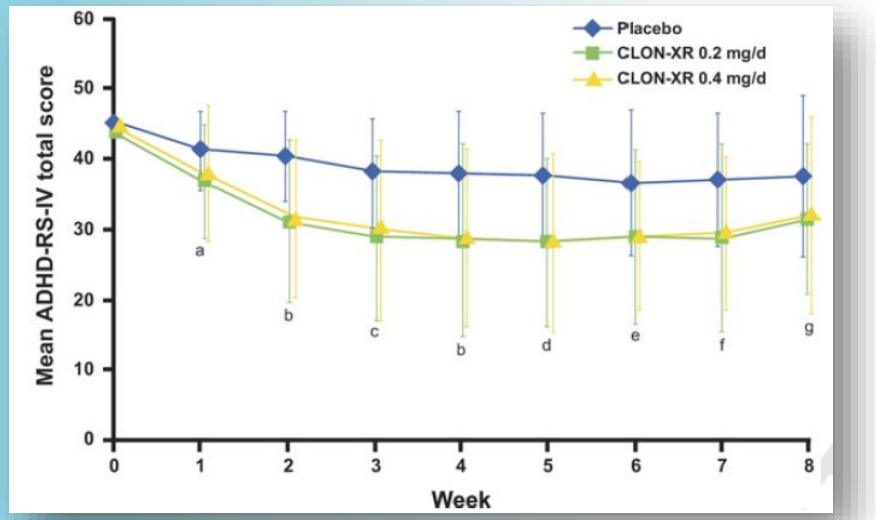
Mean ADHD Rating Scale—IV (ADHD-RS-IV) total score from baseline to Week 5, using a last observation carried forward (LOCF) method:



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* ≤.0288 for both groups.

N=236; 61% completion rate
Jain et al. *JAACAP.* epub 2011.

Guanfacine XR in Adolescent ADHD

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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

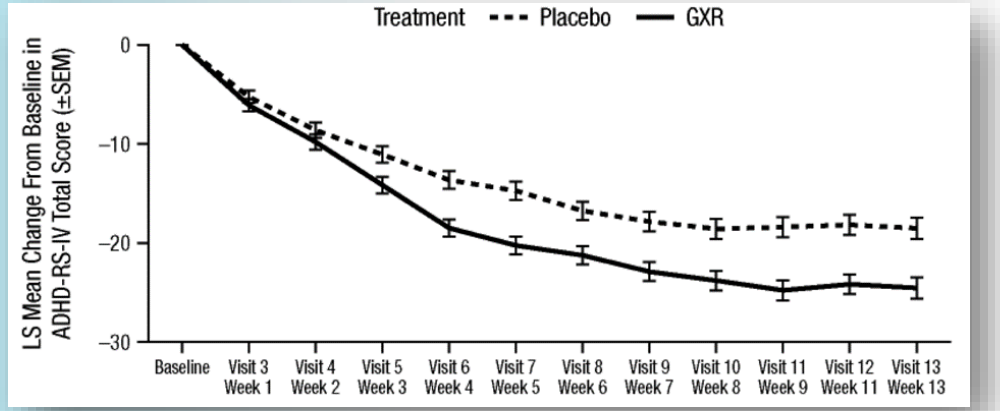
This 13-week, multicenter, randomized, double-blind, placebo-controlled trial evaluated once-daily GXR (1–7 mg per day) in adolescents with ADHD aged 13 to 17 years. The primary endpoint was the change from baseline in the ADHD Rating Scale–IV (ADHD-RS-IV) total score; key secondary endpoints included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

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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

- **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 follow-up 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 (see next slide)

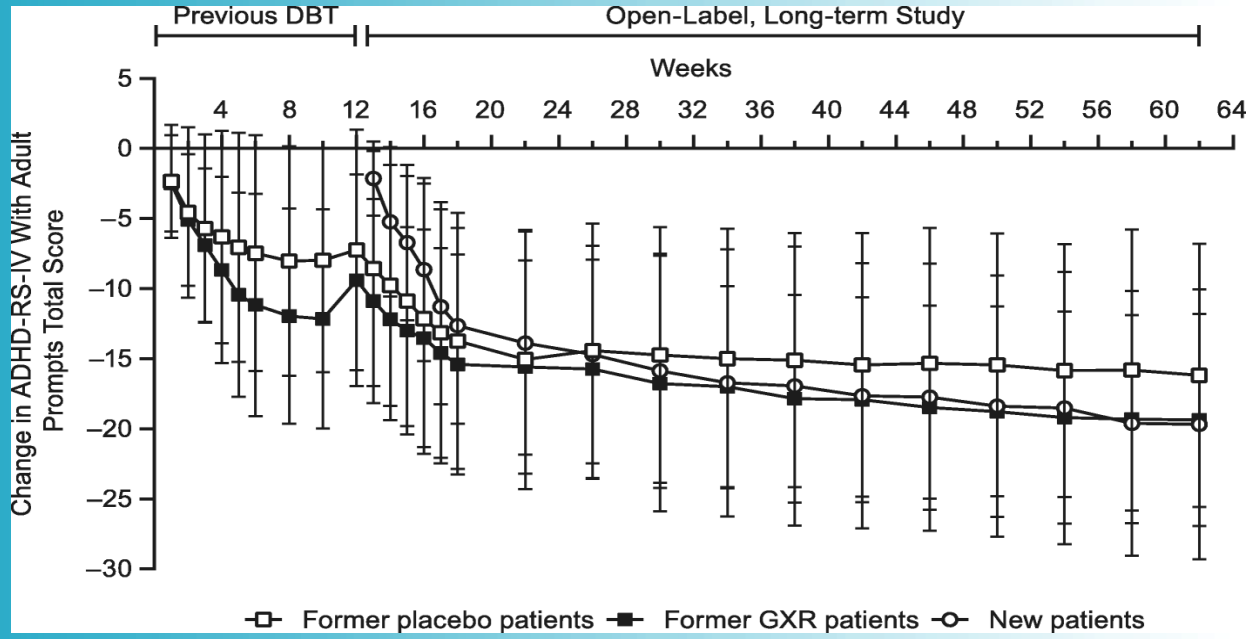
- Improved ADHD RS IV (ADHD symptoms) throughout study
- Most response in first 6 weeks; no tolerance

Adverse effects

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

Iwanami et al. *BMC Psychiatry*. 2020;Vol. 20:485.

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. *BMC Psychiatry*. 2020;Vol. 20:485.

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)

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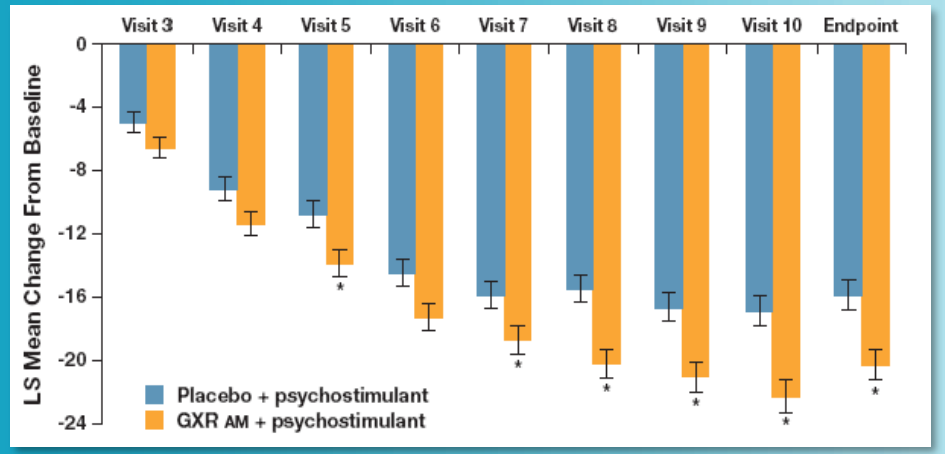
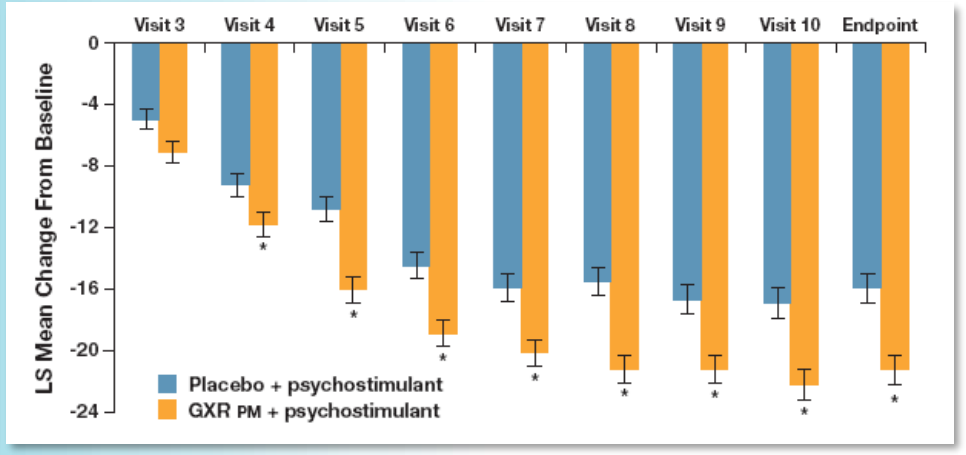
Change in ADHD-RS-IV Total Score from Baseline by Visit (FAS)

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 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.

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

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- Metanalysis of 10 studies (N=699 children)
  - 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

*Not FDA approved for ADHD

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).

Akili Announces FDA Clearance of EndeavorRx™ for Children with ADHD, the First Prescription Treatment Delivered Through a Video Game

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BOSTON, Mass – June 15, 2020 – Akili today announced that the U.S. Food and Drug Administration (FDA) has granted clearance for EndeavorRx™ (AKL-T01) as a prescription treatment for children with attention-deficit/hyperactivity disorder (ADHD). Delivered through a captivating video game experience, EndeavorRx is indicated to improve attention function as measured by computer-based testing in children ages 8-12 years old with primarily inattentive or combined-type ADHD, who have a demonstrated attention issue. See full indication below. Persistent attention issues have a significant impact on the daily lives of millions of people. Attention impairments are a key component of ADHD for many children yet are often overshadowed by more overt symptoms of ADHD.

Trigeminal Nerve Stimulation for ADHD

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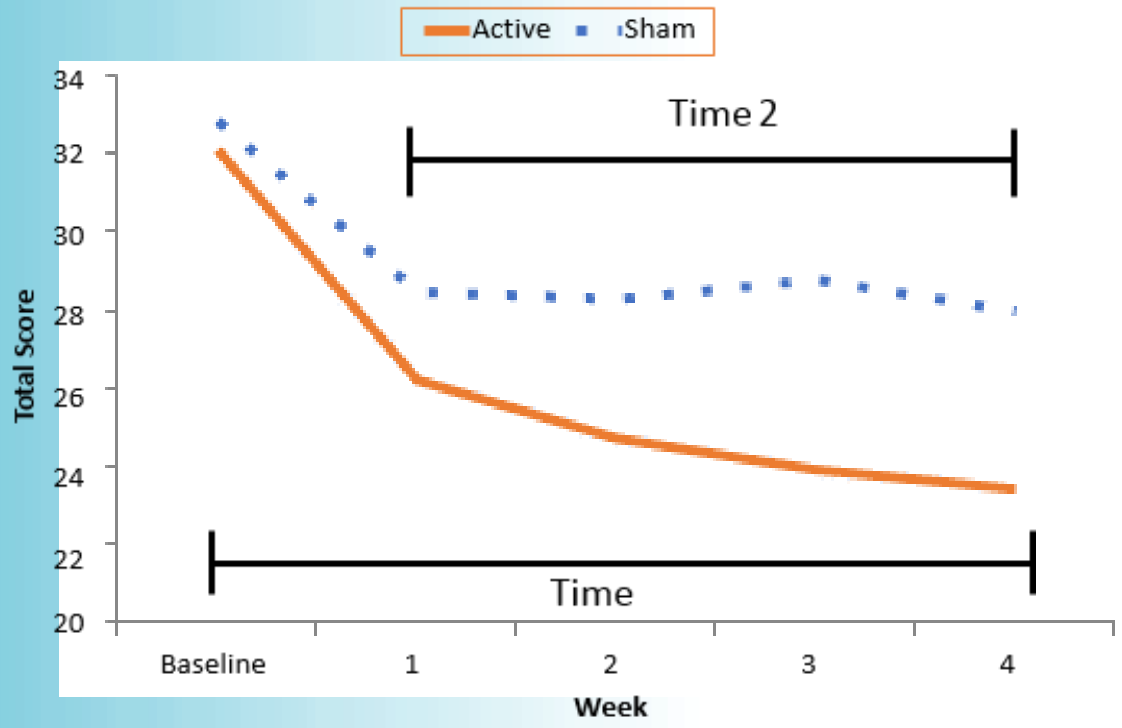
ADHD RS Over 4-week Trial
Active (N=32) Versus Sham (N=30) Trigeminal Nerve Stimulation



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

Summary: Non-Stimulant Pharmacotherapy of ADHD

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- A number of non-stimulant medications and emerging neuro devices for ADHD
- Often somewhat lower effect size than stimulants
- A variety of effective drugs
  - Noradrenergic agents (ATMX, VIL) – (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 and devices in development