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Treating ADHD Through the Lifespan: Focus on Adults

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Faculty Disclosure

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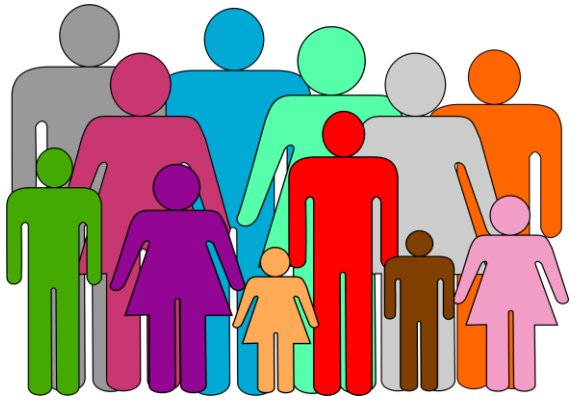
Timothy Wilens, MD has served as a consultant, or has received grant support from the following

- FDA, NIH (NIDA), 3D Therapeutics
  Licensing agreements with Ironshore (Before School Functioning Questionnaire), 3D Therapeutics
- Clinical care: MGH, Bay Cove, Gavin, National Football League, Major/Minor League Baseball
- (Co)Edited Straight Talk About Psychiatric Medications for Kids (Guilford); ADHD Across the Lifespan (Cambridge), Update in 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 (eg, substance use disorders)

ADHD Overview



- ADHD prevalence among 8- to 15-year-olds: 8.7%
- ADHD prevalence among 18- to 44-year-olds: 4.4%
- Associated with chronic course
  - Circa 75% persistence from childhood into adolescence
  - Circa 50% persistence from childhood into adulthood

Froehlich TE, et al. *Arch Pediatr Adolesc Med*. 2007;161(9):857-864.
Kessler RC, et al. *Am J Psychiatry*. 2006;163(4):716-723.
Wilens TE, et al. *Postgrad Med*. 2010;122(5):97-109.
Faraone, et al. *Nature Neuroscience*, 2015.
2021 International Consensus Statement on ADHD.

The World Federation of ADHD International Consensus Statement: 208 Evidence-Based Conclusions About the Disorder

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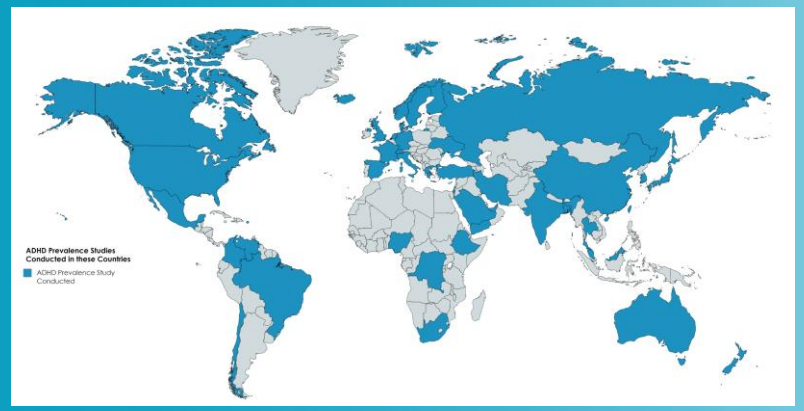

Abstract

Background: Misconceptions about ADHD stigmatize affected people, reduce credibility of providers, and prevent/delay treatment. To challenge misconceptions, we curated findings with strong evidence base.

Methods: We reviewed studies with more than 2000 participants or meta-analyses from five or more studies or 2000 or more participants. We excluded meta-analyses that did not assess publication bias, except for meta-analyses of prevalence. For network meta-analyses we required comparison adjusted funnel plots. We excluded treatment studies with waiting-list or treatment as usual controls. From this literature, we extracted evidence-based assertions about the disorder.

Results: We generated 208 empirically supported statements about ADHD. The status of the included statements as empirically supported is approved by 80 authors from 27 countries and 6 continents. The contents of the manuscript are endorsed by 366 people who have read this document and agree with its contents.

Conclusions: Many findings in ADHD are supported by meta-analysis. These allow for firm statements about the nature, course, outcome causes, and treatments for disorders that are useful for reducing misconceptions and stigma.

Keywords: ADHD; Brain; Course; Diagnosis; Genetics; Outcome; Treatment.

Neurosci Biobehav Rev. 2021 Sep;128:789-818. doi: 10.1016/j.neubiorev.2021.01.022. Epub 2021 Feb 4.

Stephen V Faraone, Tobias Banaschewski, David Coghill, et al.

Diagnosis of ADHD

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- Developmentally inappropriate symptoms
  - 6/9 Symptoms of Inattention, Hyperactivity or Combination
  - 5/9 if ≥17 years of age (adult)
  - 95% of cases are either combined or inattentive subtype
- Age of onset ≤12 years
- Not accounted for by other disorder
  - Can make diagnosis of Autism Spectrum and ADHD
- Diagnosis Clinically Derived
- Rating Scales Helpful (Parent, School)
  - WHO – ADHD (ASRS) (https://add.org/adhd-test/)
  - DSM V, Conners, Brown, Other Scales

ADHD Assessment

- Life history
- Self-report for adults
- Mental status exam
- Rating scales: measuring core and broad features
- Medical history review; cardiac and neurologic status, blood pressure/pulse
- If medical history is unremarkable, laboratory or neurological testing is not indicated
- Assess for comorbidity (psychiatric, cognitive, psychosocial, medical)

Pliszka S. AACAP Work Group on Quality Issues. *J Am Acad Child Adolesc Psychiatry*. 2007;46(7):894-921.
Huang H et al. Harvard Review of Psychiatry: 3/4 2020 - Volume 28 - Issue 2 - p 100-106.

Adult ADHD Self-Report Scale (ASRS-v1.1) Symptom Checklist

Patient Name		Today's Date					
Please answer the questions below, rating yourself on each of the criteria shown using the scale on the right side of the page. As you answer each question, place an X in the box that best describes how you have felt and conducted yourself over the past 6 months. Please give this completed checklist to your healthcare professional to discuss during today's appointment.			Never	Rarely	Sometimes	Often	Very Often
1. How often do you have trouble wrapping up the final details of a project, once the challenging parts have been done?							
2. How often do you have difficulty getting things in order when you have to do a task that requires organization?							
3. How often do you have problems remembering appointments or obligations?							
4. When you have a task that requires a lot of thought, how often do you avoid or delay getting started?							
5. How often do you fidget or squirm with your hands or feet when you have to sit down for a long time?							
6. How often do you feel overly active and compelled to do things, like you were driven by a motor?							
							Part A
7. How often do you make careless mistakes when you have to work on a boring or difficult project?							
8. How often do you have difficulty keeping your attention when you are doing boring or repetitive work?							
9. How often do you have difficulty concentrating on what people say to you, even when they are speaking to you directly?							
10. How often do you misplace or have difficulty finding things at home or at work?							
11. How often are you distracted by activity or noise around you?							
12. How often do you leave your seat in meetings or other situations in which you are expected to remain seated?							
13. How often do you feel restless or fidgety?							
14. How often do you have difficulty unwinding and relaxing when you have time to yourself?							
15. How often do you find yourself talking too much when you are in social situations?							
16. When you're in a conversation, how often do you find yourself finishing the sentences of the people you are talking to, before they can finish them themselves?							
17. How often do you have difficulty waiting your turn in situations when turn taking is required?							
18. How often do you interrupt others when they are busy?							
							Part B

WHO ADHD Screener.

Real-Life Consequences of ADHD

Biederman J et al. *J Clin Psychiatry*. 2006;67(4):524-540.
Biederman J, Faraone SV. *Med Gen Med*. 2006;8(3):12.

Heritability of ADHD

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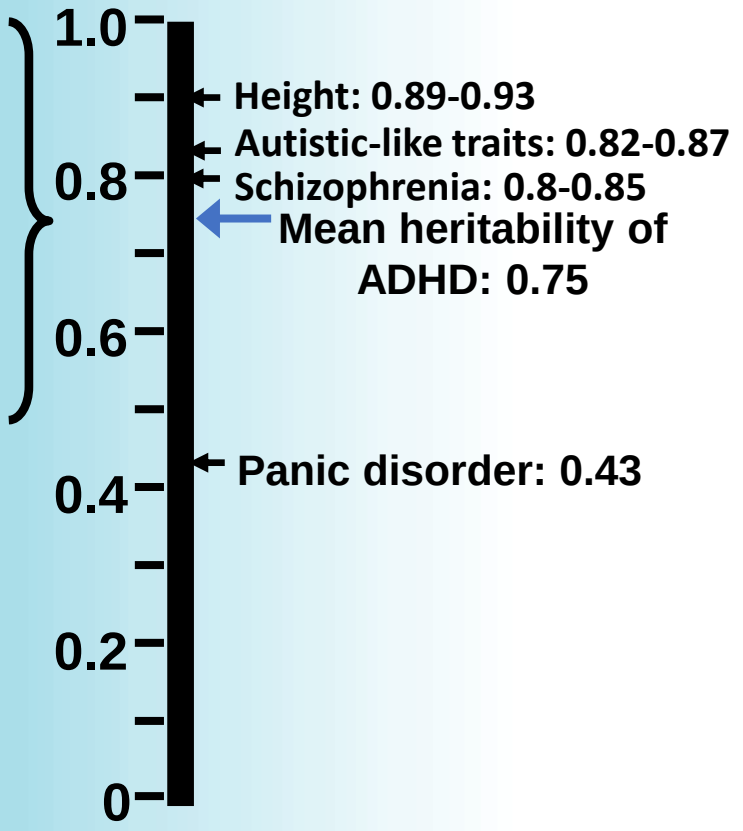
Heritability of ADHD between 0.9 and 1.0
Willcutt, 2000; Levy, 1997; Gillis, 1992

Heritability of ADHD between 0.8 and 0.9
Coolidge, 2000; Thapar, 2000; Thapar 1995

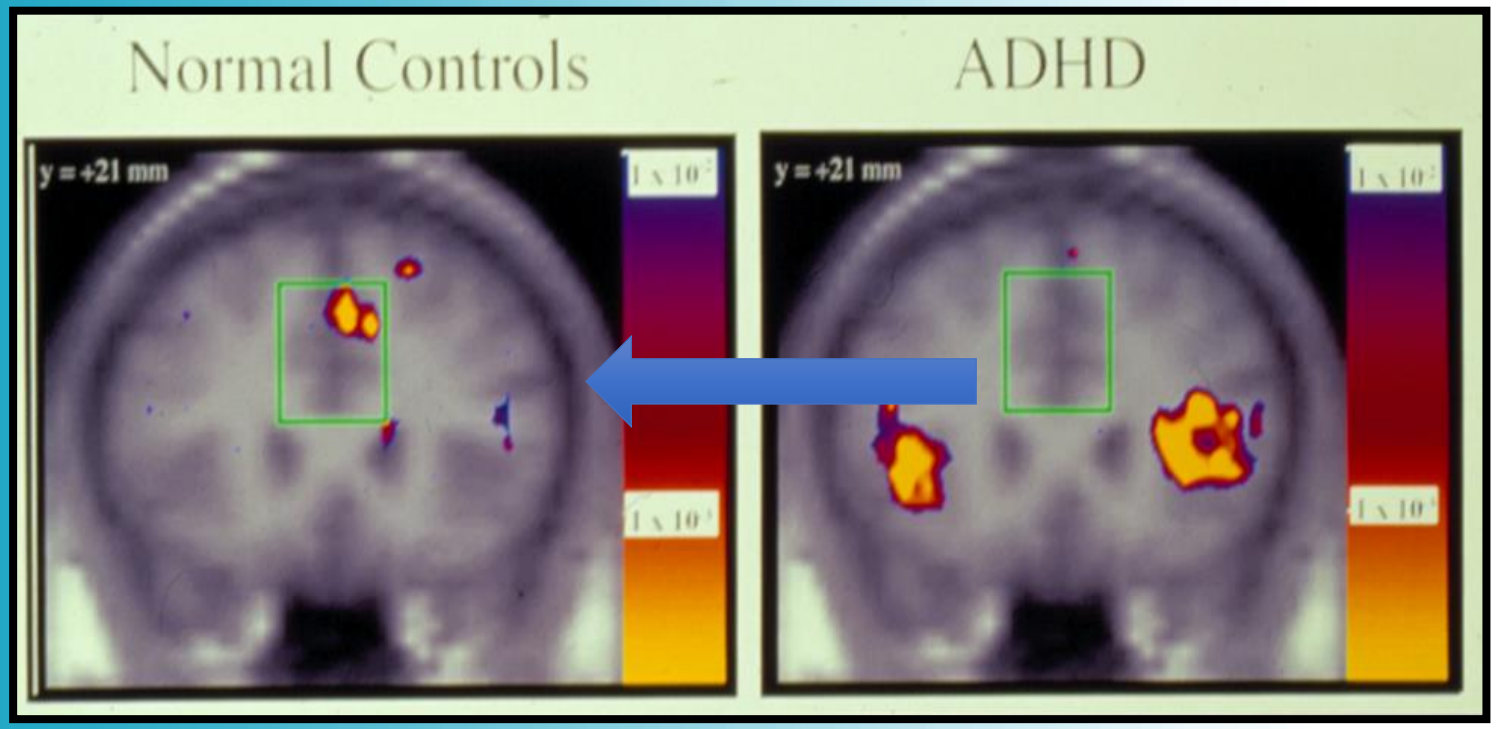
Heritability of ADHD between 0.7 and 0.8
Rietveld, 2003; Martin, 2002; Sherman, 1997; Gjone, 1996; Stevenson, 1992; Willerman, 1973; Matheny, 1971

Heritability of ADHD between 0.6 and 0.7
Kuntsi, 2001; Hudziak, 2000; Nadder, 1998; Silberg, 1996; Schmitz, 1995; Edelbrock, 1992; Goodman, 1989



Faraone SV et al. *Biol Psychiatry*. 2005;57(11):1313-1323.
Hettema JM et al. *Am J Psychiatry*. 2001;158(10):1568-1578.
Cardno AG, Gottesman II. *Am J Med Genet*. 2000;97(1):12-17.
Ronald A et al. *Eur Child Adolesc Psychiatry*. 2008;17(8):473-483.
Silventoinen K et al. *Twin Res*. 2003;6(5):399-408.

fMRI in Adults With ADHD



MGH NMR Center and Harvard-MIT CITP.
fMRI, functional magnetic resonance imaging.
Bush G et al. *Biol Psychiatry*. 1999;45(12):1542-1552
Bush G et al. *Arch Gen Psychiatry*. 2008;65(1):102-114.

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What's New on the Pharmacotherapy of ADHD in Adults?

Medications: Attention-Deficit/ Hyperactivity Disorder

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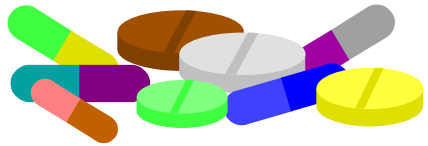

Pharmacological Treatment

Stimulants ← FDA Approved
- Methylphenidate
- Amphetamines

Noradrenergic agents ← FDA Approved
- Atomoxetine
- Viloxazine XR

Alpha Agonists ← FDA Approved
- Guanfacine (XR)
- Clonidine (XR)
- Guan XR or Clon XR + stimulants ← FDA Approved

Antidepressants
- Bupropion
- Tricyclics

Combination/others
- Modafinil
- Memantine

Newcorn & Wilens. *Child Adolesc Psych Clin N Am*. Elsevier Press 2022. www.drugs.com

Methylphenidate (MPH) in ADHD

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Medication	Starting Dose	Maximum Dose*	Duration
Ritalin IR®	5 mg QD/BID	2 mg/kg/day	4 hr / BID
Focalin®	2.5 mg QD/BID	1 mg/kg/day	4–5 hr / BID–TID
Focalin XR®	5 mg QD	1 mg/kg/day	10–12 hr QD
Daytrana®	10 mg		6–16 hr
Concerta®	18 mg QD	2 mg/kg/day	12 hr / once
Metadate CD®	20 mg QD		8 hr / once
Ritalin LA®	20 mg QD		8 hr / once
Quillivant XR®	<10 mg QD		12 hr / once
Quillichew ER®	<10 mg QD		8 hr / once
Cotempla XR-ODT® (disintegrating tab)	8.6 mg QD	51.8 mg	12 hr / once
Aptensio XR®	10 mg QD	2 mg/kg/day	12 hr / once
Adhansia XR®	25 mg QD		12 hr / once
Jornay PM® (delayed release)	20 mg QD	100 mg	12 hr / once
Azstarys™ (serdexMPH, MPH)	26.1/5.2 mg QD	52.3/10.4 mg	13 hr / once

*May exceed FDA approved dose.

Update in the Pharmacotherapy of ADHD. *Child Adolesc Psych Clin N Am*. Newcorn & Wilens (eds). Elsevier Press, 2022. www.drugs.com. US Food and Drug Administration. Drugs@FDA: FDA Approved Drug Products. www.accessdata.fda.gov/scripts/cder/daf/.

Amphetamine (AMPH) in ADHD

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Medication	Starting Dose	Maximum Dose* Usual Dosing	Duration
Adderall®	2.5–5 mg QD	1.5 mg/kg/day	6 hr / BID
Adderall XR®	2.5–5 mg QD		12 hr / QD
Vyvanse®	30 mg QD		12–14 hr / QD
Mydayis®	12.5 mg QD	50/25 mg (adults/adolescents)	To 16 hr / QD
Dexedrine Tablets®	2.5–5 mg BID	1.5 mg/kg/day	3–5 hr / BID–QID
Evekeo®	2.5–5 mg BID		3–5 hr / BID–QID
Dexedrine Spansule®	5 mg QD		6 hr / QD–BID
Dyanavel® XR (suspension)	2.5–5 mg QD	1.5 mg/kg/day	13 hr / QD
Adzenys XR-ODT® (disintegrating tab)	6.3–12.5 mg QD	12.5 mg (adolescents)	12 hr / QD
Xelstrym (Patch)	4.5 mg		12 hr/ QD

*May exceed FDA approved dose.

Update in the Pharmacotherapy of ADHD. *Child Adolesc Psych Clin N Am.* Newcord & Wilens (eds). Elsevier Press, 2022. www.drugs.com.
US Food and Drug Administration. Drugs@FDA: FDA Approved Drug Products. www.accessdata.fda.gov/scripts/cder/daf/.

Medications: Attention-Deficit/Hyperactivity Disorder

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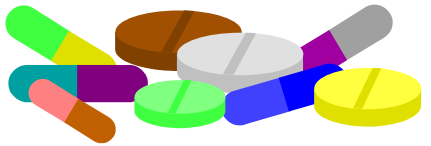
Pharmacological Treatment



Stimulants ← FDA Approved
- Methylphenidate
- Amphetamines

Atomoxetine ← FDA Approved

Viloxazine XR ← FDA Approved

Alpha Agonists ← FDA Approved
- Guanfacine (XR)
- Clonidine (XR)
- Guan XR or Clon XR + stimulants ← FDA Approved

Antidepressants
- Bupropion
- Tricyclics

Combination/others
- Memantine

Adler, Spencer, Wilens (eds). *ADHD in Children & Adults*. Cambridge Press, 2015.
Newcorn and Wilens (eds). *Psych Clin N Am.* Elsevier Press, 2022.

What to Do at Evaluation (AHA Guidelines)

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- **Medical History**
  (***essentially screening of sudden death risk***)
  - **Personal congenital or acquired cardiac disease**
  - **Palpitations, chest pain, syncope, seizures, post-exercise symptoms**
  - **Family history or premature cardiac disease (<30 yrs of age)**
  - **Other meds (including OTC)**
  - **Routine med history (neurological, etc.)**
- **BP/heart rate**
- ***Suspicion* of CV defect (e.g., ARVD, MI, SVT) --w/u as indicated**
- **Monitor above during treatment**
- **Issues of informed consent**

Gutgesell H et al. *Circulation.* 1999:99:979-982.
AAP Guidelines. 2008.
Perrin et al. *Pediatrics.* 2008.
Wilens et al. *Pediatrics.* 2006.
Cooper et al. *NEJM* 2012.
Cooper et al. *JAMA* 2012.

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 weeks dose titration, 5 weeks maintenance**

Findings

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

Adverse Effects (vs. placebo)

- **No serious AEs**
- **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.

Viloxazine for ADHD

- Noradrenergic inhibitor
- Approved in children –> adults
- Adult study- Phase III, 6 week RCT study
- N = 374 adults with ADHD
- Dosing: 200 mg, 400 mg, and 600 mg

Findings

- Improvement up to 600 mg doses
- ADHD Symptoms (RS 5), CGI

Side Effects

- Generally good tolerability
- Somnolence, decreased appetite, headache (across lifespan)

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

Non-FDA Approved, Non-Stimulants in ADHD

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- Bupropion
  - RCTs in Children (and adults)
  - Generally smaller effect size (ES) vs. stimulants
- Modafinil
  - Multiple RCTs positive in children (careful with Stevens-Johnson Syndrome)
  - Failed RCTs in adults
- Tricyclics (imipramine, nortriptyline, desipramine)
  - Multiple RCTs in children/adolescents and adults
  - Longer term persistent effect without tolerance
  - Serum levels, ECG monitoring recommended
- Memantine
  - Mainly open; RCT underway
  - (+) RCT in adults (Mohammadzadeh et al. Human Psychoharm 2019)
  - Less effective than MPH in parallel study (Iran J Psych; 2015)
  - Improvements in ADHD, executive functioning

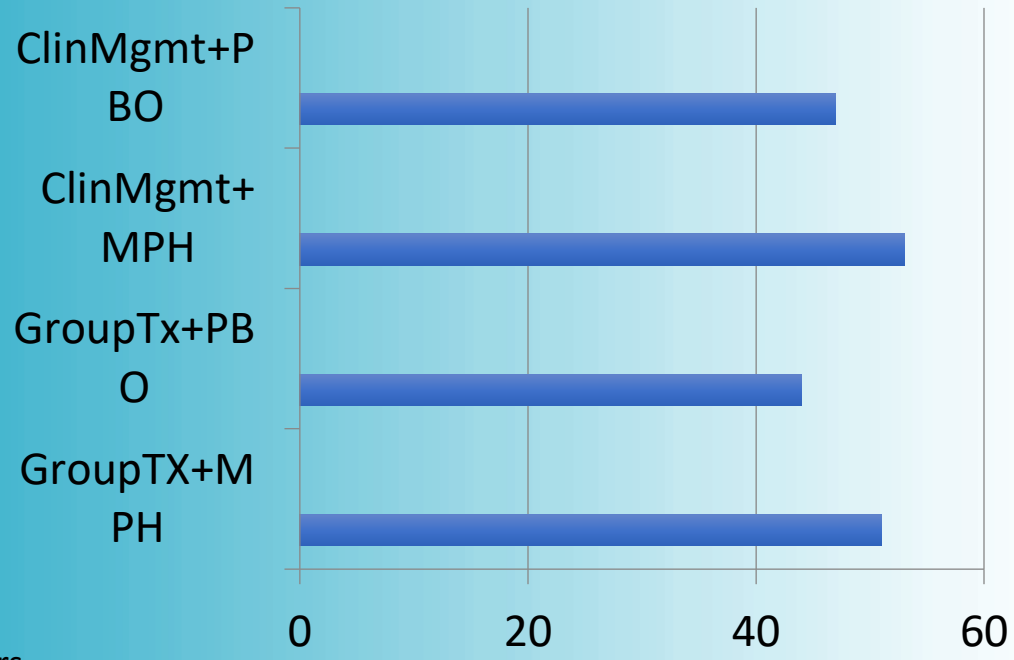
Newcorn et al. Nonstimulants in Update in Pharmacotherapy of ADHD in Newcorn and Wilens (eds). Elsevier Press, 2022.

Other Treatments?

Effects of Group Psychotherapy, Individual Counseling, Methylphenidate, and Placebo in the Treatment of ADHD in Adults

Philipsen et al. *JAMA Psychiatry*. 2015:1199-1210.

Percent Response (>30% reduction in Observer CAARS ADHD index) at 52 weeks



pNS overall % response;

For ADHD index LOCF:
MPH vs PBO p<0.001

N=419 subjects, 7 German Centers,
12 Weeks of weekly treatment then monthly thereafter; Tx to 1 year
MPH Dosing to 60 mg/day maximum (or 1.3 mg/kg/day)
For ADHD index

Randomized Controlled Trial > JAMA Psychiatry. 2022 Sep 1;79(9):847-856.
doi: 10.1001/jamapsychiatry.2022.2055.

Transcranial Direct Current Stimulation vs Sham for the Treatment of Inattention in Adults With Attention-Deficit/Hyperactivity Disorder: The TUNED Randomized Clinical Trial

Douglas Teixeira Leffa [1 2], Eugenio Horacio Grevet [1 2], Claiton Henrique Dotto Bau [1 3], Maitê Schneider [1 2], Carolina Prietto Ferrazza [1 2], Roberta Francieli da Silva [1 2], Marina Silva Miranda [1 2], Felipe Picon [1 2], Stefania Pigatto Teche [1 2], Paulo Sanches [4], Danton Pereira [4], Katya Rubia [5], André Russowsky Brunoni [6], Joan A Camprodon [7], Wolnei Caumo [8 9 10], Luis Augusto Rohde [1 2 11]

Affiliations + expand

PMID: 35921102 PMCID: PMC9350846 (available on 2023-08-03)
DOI: 10.1001/jamapsychiatry.2022.2055

Abstract

Importance: Transcranial direct current stimulation (tDCS) may improve symptoms of inattention in adults with attention-deficit/hyperactivity disorder (ADHD). However, previous trials are characterized by small sample sizes, heterogeneous methodologies, and short treatment periods using clinic-based tDCS.

Objective: To determine the efficacy and safety of home-based tDCS in treating inattention symptoms in adult patients with ADHD.

Design, setting, and participants: Randomized, double-blind, parallel, sham-controlled clinical trial (tDCS for the Treatment of Inattention Symptoms in Adult Patients With ADHD [TUNED]), conducted from July 2019 through July 2021 in a single-center outpatient academic setting. Of 277 potential participants screened by phone, 150 were assessed for eligibility on site, and 64 were included. Participants were adults with ADHD, inattentive or combined subtype. Exclusion criteria included current stimulant drug treatment, current moderate to severe symptoms of depression or anxiety, diagnosis of bipolar disorder with a manic or depressive episode in the last year, diagnosis of schizophrenia or another psychotic disorder, and diagnosis of autism spectrum disorder; 55 of participants completed follow-up after 4 weeks.

Interventions: Thirty-minute daily sessions of home-based tDCS for 4 weeks, 2 mA anodal-right and cathodal-left prefrontal stimulation with 35-cm2 carbon electrodes.

Main outcomes and measures: Inattentive scores in the clinician-administered version of the Adult ADHD Self-report Scale version 1.1 (CASRS-I).

Results: Included in this trial were 64 participants with ADHD (31 [48%] inattentive presentation and 33 [52%] combined presentation), with a mean (SD) age of 38.3 (9.6) years. Thirty participants (47%) were women and 34 (53%) were men. Fifty-five finished the trial. At week 4, the mean (SD) inattention score, as measured with CASRS-I, was 18.88 (5.79) in the active tDCS group and 23.63 (3.97) in the sham tDCS group. Linear mixed-effects models revealed a statistically significant treatment by time interaction for CASRS-I (βinteraction = -3.18; 95% CI, -4.60 to -1.75; P < .001), showing decreased symptoms of inattention in the active tDCS group over the 3 assessments compared to the sham tDCS group. Mild adverse events were more frequent in the active tDCS group, particularly skin redness, headache, and scalp burn.

Conclusions and relevance: In this randomized clinical trial, daily treatment with a home-based tDCS device over 4 weeks improved attention in adult patients with ADHD who were not taking stimulant medication. Home-based tDCS could be a nonpharmacological alternative for patients with ADHD.

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Multisite study of home based tDCS

Design: N= 64 adults with ADHD (31 [48%] inattentive presentation and 33 [52%] combined presentation)
Mean age 38.3 (9.6) years.

Findings: At week 4, the mean (SD) inattention score, as measured with CASRS-I, was 19 (5.79) in the active tDCS group and 24 (3.97) in the sham tDCS group (P < .001)

Conclusion: Home based tDCS improved inattention

Representative Experimental Pharmaceuticals for ADHD*

Effectiveness/efficacy demonstrated*

- **Dasatroline** – Biamine reuptake inhibitor
  2 adult RCT positive (*Neuropsychopharm. 2015)*
  Pediatric RCT (Findling et al. *J Child Adoles Psychopharm. 2019)*
- **Centanafadine** – Triamine reuptake inhibitor significant effects in adults (Wigal et al. 2020)
- **Molindone** – Impulse/ADHD; antipsychotic; child/adults
  Phase 3 studies (Britain et al. *Neurol. 2016)*
- **Mazindol** – Catecholamine reuptake inhibitor (Wigal et al. *CNS Drugs*. 2018)
- **New stimulant preparations** (multiple)
  - Release systems
  - Prodrugs
  - Abuse deterrence

*Not FDA approved for ADHD
Newcorn et al. Nonstimulants. *Pharmacotherapy of ADHD.* Elsevier 2022.

Conclusions

- ADHD is considered a lifespan disorder
- Careful assessment of ADHD and associated psychiatric, psychosocial, and medical comorbidities is necessary prior to initiating treatment
- Consider the implications of not treating ADHD
- Psychosocial interventions can be an important part of the treatment
- Treatment with both stimulants and nonstimulants demonstrated both effective and safe
- Management requires ongoing reassessment and intervention