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PSYCHIATRY ACADEMY

Treatment of Adults with ADHD

Timothy E. Wilens, MD

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Professor of Psychiatry, Harvard Medical School

Faculty Disclosure

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

- NIH (NIDA), Food and Drug Administration
- Licensing agreement with 3D Therapy
- Clinical care: MGH, Bay Cove Human Services, Gavin, Major/Minor League Baseball
- (Co)Edited Straight Talk About Psychiatric Medications for Kids (Guilford); 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)

Medications: Attention-Deficit/ Hyperactivity Disorder

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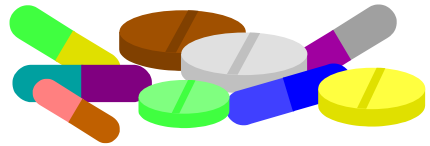

Pharmacological Treatment

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/.

More Switching from Initial Choice of MPH than Amph

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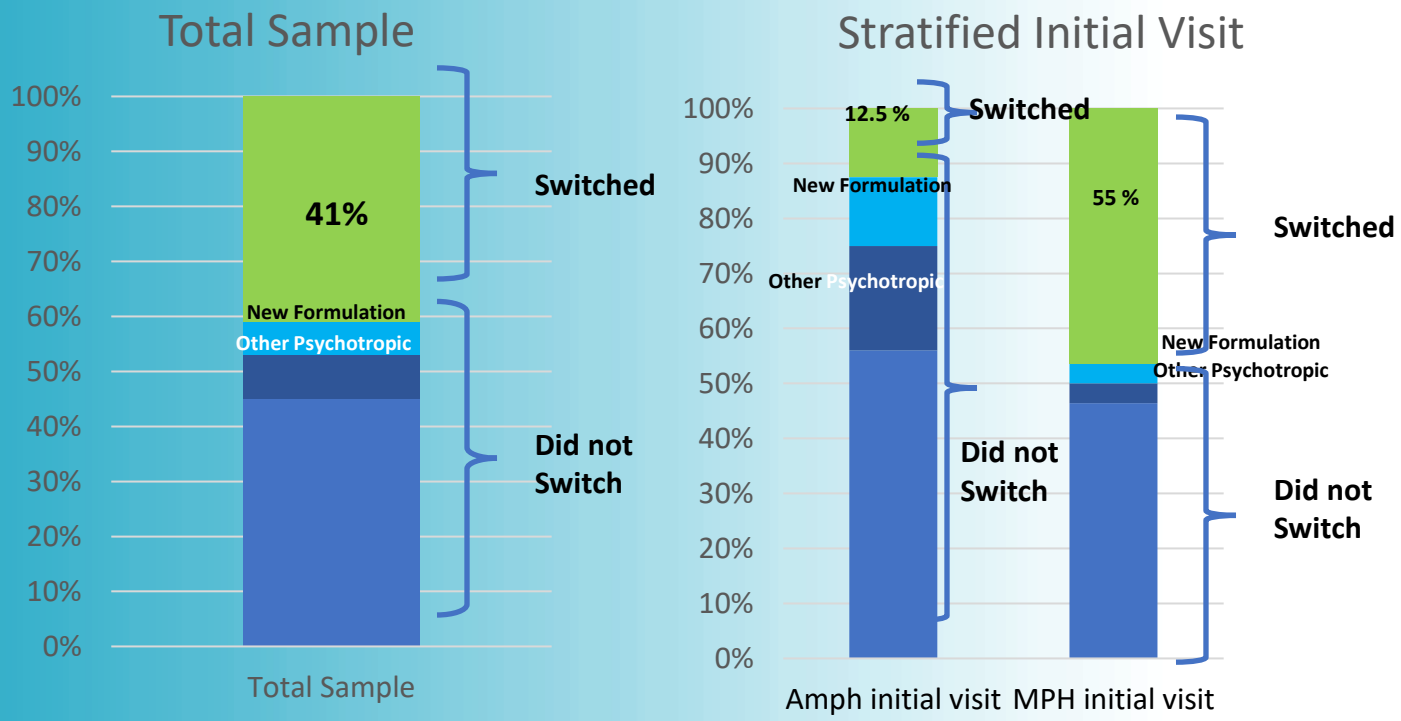
N= 49 Unmedicated Adults with ADHD



Biederman et al. Psychopharmacology 2021

Medications: Attention-Deficit/Hyperactivity Disorder

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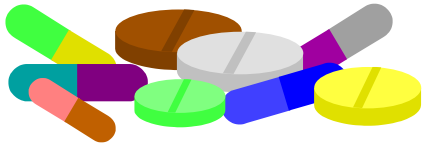
Pharmacological Treatment



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.

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
  - (+) 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 (Biederman et al, 2020)

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

JAMA Psychiatry | Original Investigation

Attention-Deficit/Hyperactivity Disorder Medications and Long-Term Risk of Cardiovascular Diseases

Le Zhang, PhD; Lin Li, PhD; Pontus Andell, MD, PhD; Miguel Garcia-Argibay, PhD; Patrick D. Quinn, PhD; Brian M. D'Onofrio, PhD; Isabell Brikell, PhD; Ralf Kuja-Halkola, PhD; Paul Lichtenstein, PhD; Kristina Johnell, PhD; Henrik Larsson, PhD; Zheng Chang, PhD

IMPORTANCE Use of attention-deficit/hyperactivity disorder (ADHD) medications has increased substantially over the past decades. However, the potential risk of cardiovascular disease (CVD) associated with long-term ADHD medication use remains unclear.

OBJECTIVE To assess the association between long-term use of ADHD medication and the risk of CVD.

DESIGN, SETTING, AND PARTICIPANTS This case-control study included individuals in Sweden aged 6 to 64 years who received an incident diagnosis of ADHD or ADHD medication dispensation between January 1, 2007, and December 31, 2020. Data on ADHD and CVD diagnoses and ADHD medication dispensation were obtained from the Swedish National Inpatient Register and the Swedish Prescribed Drug Register, respectively. Cases included individuals with ADHD and an incident CVD diagnosis (ischemic heart diseases, cerebrovascular diseases, hypertension, heart failure, arrhythmias, thromboembolic disease, arterial disease, and other forms of heart disease). Incidence density sampling was used to match cases with up to 5 controls without CVD based on age, sex, and calendar time. Cases and controls had the same duration of follow-up.

EXPOSURE Cumulative duration of ADHD medication use up to 14 years.

MAIN OUTCOMES AND MEASURES The primary outcome was incident CVD. The association between CVD and cumulative duration of ADHD medication use was measured using adjusted odds ratios (AORs) with 95% CIs.

RESULTS Of 278 027 individuals with ADHD aged 6 to 64 years, 10 388 with CVD were identified (median [IQR] age, 34.6 [20.0-45.7] years; 6154 males [59.2%]) and matched with 51 672 control participants without CVD (median [IQR] age, 34.6 [19.8-45.6] years; 30 601 males [59.2%]). Median (IQR) follow-up time in both groups was 4.1 (1.9-6.8) years. Longer cumulative duration of ADHD medication use was associated with an increased risk of CVD compared with nonuse (0 to ≤1 year: AOR, 0.99 [95% CI, 0.93-1.06]; 1 to ≤2 years: AOR, 1.09 [95% CI, 1.01-1.18]; 2 to ≤3 years: AOR, 1.15 [95% CI, 1.05-1.25]; 3 to ≤5 years: AOR, 1.27 [95% CI, 1.17-1.39]; and >5 years: AOR, 1.23 [95% CI, 1.12-1.36]). Longer cumulative ADHD medication use was associated with an increased risk of hypertension (eg, 3 to ≤5 years: AOR, 1.72 [95% CI, 1.51-1.97] and >5 years: AOR, 1.80 [95% CI, 1.55-2.08]) and arterial disease (eg, 3 to ≤5 years: AOR, 1.65 [95% CI, 1.11-2.45] and >5 years: AOR, 1.49 [95% CI, 0.96-2.32]). Across the 14-year follow-up, each 1-year increase of ADHD medication use was associated with a 4% increased risk of CVD (AOR, 1.04 [95% CI, 1.03-1.05]), with a larger increase in risk in the first 3 years of cumulative use (AOR, 1.08 [95% CI, 1.04-1.11]) and stable risk over the remaining follow-up. Similar patterns were observed in children and youth (aged <25 years) and adults (aged ≥25 years).

CONCLUSIONS AND RELEVANCE This case-control study found that long-term exposure to ADHD medications was associated with an increased risk of CVDs, especially hypertension and arterial disease. These findings highlight the importance of carefully weighing potential benefits and risks when making treatment decisions about long-term ADHD medication use. Clinicians should regularly and consistently monitor cardiovascular signs and symptoms throughout the course of treatment.

JAMA Psychiatry. 2024;81(2):178-187. doi:10.1001/jamapsychiatry.2023.4294

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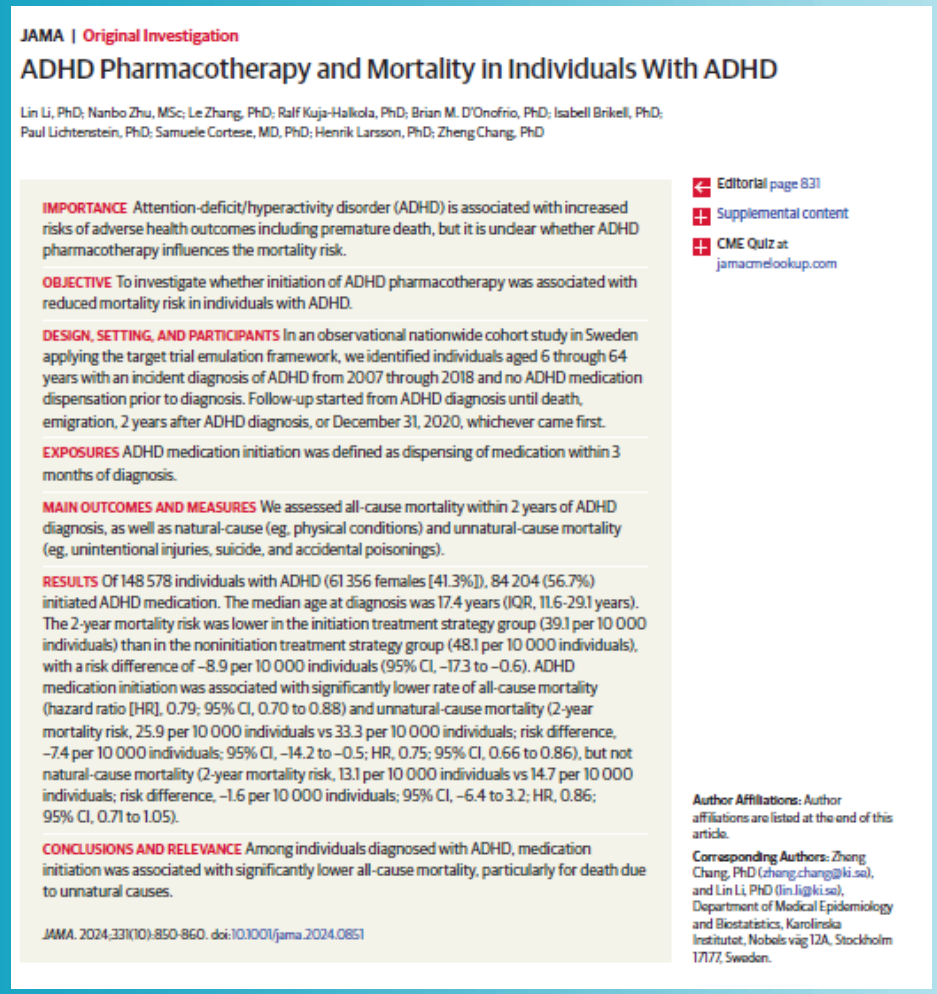
Design
Swedish registry study
N=278,027 (6-64 yrs)
Mean 4 yr follow-up
2007-2020

Findings:
10,388 (3.7%) with CVD (cardiovascular disease)
Longer duration meds-more CVD
Hypertension main finding>arterial disease
Each 1 yr (only for 3 yrs) increased risk

Caveat:
Retrospective matching
Main finding hypertension
Recent study from same group-lower mortality



JAMA | Original Investigation

ADHD Pharmacotherapy and Mortality in Individuals With ADHD

Lin Li, PhD; Nanbo Zhu, MSc; Le Zhang, PhD; Ralf Kuja-Halkola, PhD; Brian M. D'Onofrio, PhD; Isabell Brikell, PhD; Paul Lichtenstein, PhD; Samuele Cortese, MD, PhD; Henrik Larsson, PhD; Zheng Chang, PhD

IMPORTANCE Attention-deficit/hyperactivity disorder (ADHD) is associated with increased risks of adverse health outcomes including premature death, but it is unclear whether ADHD pharmacotherapy influences the mortality risk.

OBJECTIVE To investigate whether initiation of ADHD pharmacotherapy was associated with reduced mortality risk in individuals with ADHD.

DESIGN, SETTING, AND PARTICIPANTS In an observational nationwide cohort study in Sweden applying the target trial emulation framework, we identified individuals aged 6 through 64 years with an incident diagnosis of ADHD from 2007 through 2018 and no ADHD medication dispensation prior to diagnosis. Follow-up started from ADHD diagnosis until death, emigration, 2 years after ADHD diagnosis, or December 31, 2020, whichever came first.

EXPOSURES ADHD medication initiation was defined as dispensing of medication within 3 months of diagnosis.

MAIN OUTCOMES AND MEASURES We assessed all-cause mortality within 2 years of ADHD diagnosis, as well as natural-cause (eg, physical conditions) and unnatural-cause mortality (eg, unintentional injuries, suicide, and accidental poisonings).

RESULTS Of 148 578 individuals with ADHD (61 356 females [41.3%]), 84 204 (56.7%) initiated ADHD medication. The median age at diagnosis was 17.4 years (IQR, 11.6-29.1 years). The 2-year mortality risk was lower in the initiation treatment strategy group (39.1 per 10 000 individuals) than in the noninitiation treatment strategy group (48.1 per 10 000 individuals), with a risk difference of −8.9 per 10 000 individuals (95% CI, −17.3 to −0.6). ADHD medication initiation was associated with significantly lower rate of all-cause mortality (hazard ratio [HR], 0.79; 95% CI, 0.70 to 0.88) and unnatural-cause mortality (2-year mortality risk, 25.9 per 10 000 individuals vs 33.3 per 10 000 individuals; risk difference, −7.4 per 10 000 individuals; 95% CI, −14.2 to −0.5; HR, 0.75; 95% CI, 0.66 to 0.86), but not natural-cause mortality (2-year mortality risk, 13.1 per 10 000 individuals vs 14.7 per 10 000 individuals; risk difference, −1.6 per 10 000 individuals; 95% CI, −6.4 to 3.2; HR, 0.86; 95% CI, 0.71 to 1.05).

CONCLUSIONS AND RELEVANCE Among individuals diagnosed with ADHD, medication initiation was associated with significantly lower all-cause mortality, particularly for death due to unnatural causes.

JAMA. 2024;331(10):850-860. doi:10.1001/jama.2024.0851

Editorial page 831
Supplemental content
CME Quiz at jamacmelookup.com

Author Affiliations: Author affiliations are listed at the end of this article.

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Design:

Swedish study 2007-2018
Ages 6-64 years with ADHD
148 578 individuals with ADHD
84 204 (57%) initiated ADHD medication
F/u ADHD to death, 2 yrs post ADHD Dx, lost to f/u

Findings:

Lower mortality in treated vs untreated groups
ADHD medication associated with HR 0.79 for all cause mortality (especially unnatural causes)

Conclusion:

Lower mortality associated with ADHD treatment

ADHD Meds are Not Associated with Adverse Cardiovascular Outcomes in Adults

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ADHD Medications and Risk of Serious Cardiovascular Events in Young and Middle-aged Adults

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Colin M. Sox, MD, MS
K. Arnold Chan, MD, ScD
Bruce H. Fireman, MA
Patrick G. Arbogast, PhD
T. Craig Cheetham, PharmD, MS
Virginia P. Quinn, PhD, MPH
Sascha Dublin, MD, PhD
Denise M. Boudreau, PhD, RPh
Susan E. Andrade, ScD
Pamala A. Pawloski, PharmD
Marsha A. Raebel, PharmD
David H. Smith, RPh, PhD
Ninah Achacoso, MS
Connie Uratsu, RN
Alan S. Go, MD
Steve Sidney, MD, MPH
Mai N. Nguyen-Huynh, MD, MAS
Wayne A. Ray, PhD
Joe V. Selby, MD, MPH

Context More than 1.5 million US adults use stimulants and other medications labeled for treatment of attention-deficit/hyperactivity disorder (ADHD). These agents can increase heart rate and blood pressure, raising concerns about their cardiovascular safety.

Objective To examine whether current use of medications prescribed primarily to treat ADHD is associated with increased risk of serious cardiovascular events in young and middle-aged adults.

Design, Setting, and Participants Retrospective, population-based cohort study using electronic health care records from 4 study sites (OptumInsight Epidemiology, Tennessee Medicaid, Kaiser Permanente California, and the HMO Research Network), starting in 1986 at 1 site and ending in 2005 at all sites, with additional covariate assessment using 2007 survey data. Participants were adults aged 25 through 64 years with dispensed prescriptions for methylphenidate, amphetamine, or atomoxetine at baseline. Each medication user (n=150 359) was matched to 2 nonusers on study site, birth year, sex, and calendar year (443 198 total users and nonusers).

Main Outcome Measures Serious cardiovascular events, including myocardial infarction (MI), sudden cardiac death (SCD), or stroke, with comparison between current or new users and remote users to account for potential healthy-user bias.

Results During 806 182 person-years of follow-up (median, 1.3 years per person), 1357 cases of MI, 296 cases of SCD, and 575 cases of stroke occurred. There were 107 322 person-years of current use (median, 0.33 years), with a crude incidence per 1000 person-years of 1.34 (95% CI, 1.14-1.57) for MI, 0.30 (95% CI, 0.20-0.42) for SCD, and 0.56 (95% CI, 0.43-0.72) for stroke. The multivariable-adjusted rate ratio (RR) of serious cardiovascular events for current use vs nonuse of ADHD medications was 0.83 (95% CI, 0.72-0.96). Among new users of ADHD medications, the adjusted RR was 0.77 (95% CI, 0.63-0.94). The adjusted RR for current use vs remote use was 1.03 (95% CI, 0.86-1.24); for new use vs remote use, the adjusted RR was 1.02 (95% CI, 0.82-1.28); the upper limit of 1.28 corresponds to an additional 0.19 events per 1000 person-years at ages 25-44 years and 0.77 events per 1000 person-years at ages 45-64 years.

Conclusions Among young and middle-aged adults, current or new use of ADHD medications, compared with nonuse or remote use, was not associated with an increased risk of serious cardiovascular events. Apparent protective associations likely represent healthy-user bias.

JAMA. 2011;306(24):doi:10.1001/jama.2011.1830 www.jama.com

BETWEEN 2001 AND 2010, USE of medications labeled for treatment of attention-deficit/hyperactivity disorder (ADHD) increased even more rapidly in adults

Habel et al. *JAMA* 2011; 306(24) 2673-2683.

Cardiopulmonary Exercise Testing: MGH Study of Amphetamines in Adults with ADHD

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MGH Protocol - Electronically braked ergometer, 12-lead ECG Metabolic cart (MedGraphics)

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.

JAMA Psychiatry | Original Investigation

Prescription Stimulant Use During Pregnancy and Risk of Neurodevelopmental Disorders in Children

Elizabeth A. Suarez, MPH, PhD; Brian T. Bateman, MD, MS; Sonia Hernandez-Diaz, MD, DrPH; Loreen Straub, MD, MS; Christopher J. McDougle, MD; Katherine L. Wisner, MD, MS; Kathryn J. Gray, MD, PhD;

Conclusions

The results of this cohort study of pregnant individuals and their children in 2 large health care utilization databases in the US suggest that in utero exposure to amphetamine/dextroamphetamine and methylphenidate are not associated with an increase in neurodevelopmental disorders in children

included 1 773 501 stimulant-unexposed, 2372 amphetamine/dextroamphetamine-exposed, and 337 methylphenidate-exposed pregnancies with a mean (SD) age of 31.6 (4.6) years. In unadjusted analyses, amphetamine/dextroamphetamine and methylphenidate exposure were associated with a 2- to 3-fold increased risk of the neurodevelopmental outcomes considered. After adjustment for measured confounders, amphetamine/dextroamphetamine exposure was not associated with any outcome (autism spectrum disorder: hazard ratio [HR], 0.80; 95% CI, 0.56-1.14]; ADHD: HR, 1.07; 95% CI, 0.89-1.28; any neurodevelopmental disorder: HR, 0.91; 95% CI, 0.81-1.28). Methylphenidate exposure was associated with an increased risk of ADHD (HR, 1.43; 95% CI, 1.12-1.82]) but not other outcomes after adjustment (autism spectrum disorder: HR, 1.06; 95% CI, 0.62-1.81; any neurodevelopmental disorder: HR, 1.15; 95% CI, 0.97-1.36). The association between methylphenidate and ADHD did not persist in sensitivity analyses with stricter control for confounding by maternal ADHD.

CONCLUSIONS AND RELEVANCE The findings in this study suggest that amphetamine/dextroamphetamine and methylphenidate exposure in utero are not likely to meaningfully increase the risk of childhood neurodevelopmental disorders.

JAMA Psychiatry. doi:10.1001/jamapsychiatry.2023.5073
Published online January 24, 2024.

Original Investigatic

Adult Atten

Stephen Z. Levine, PhD
Michal Schnaider Beeri,

Abstract

IMPORTANCE Evide
with an increased risl
untested.

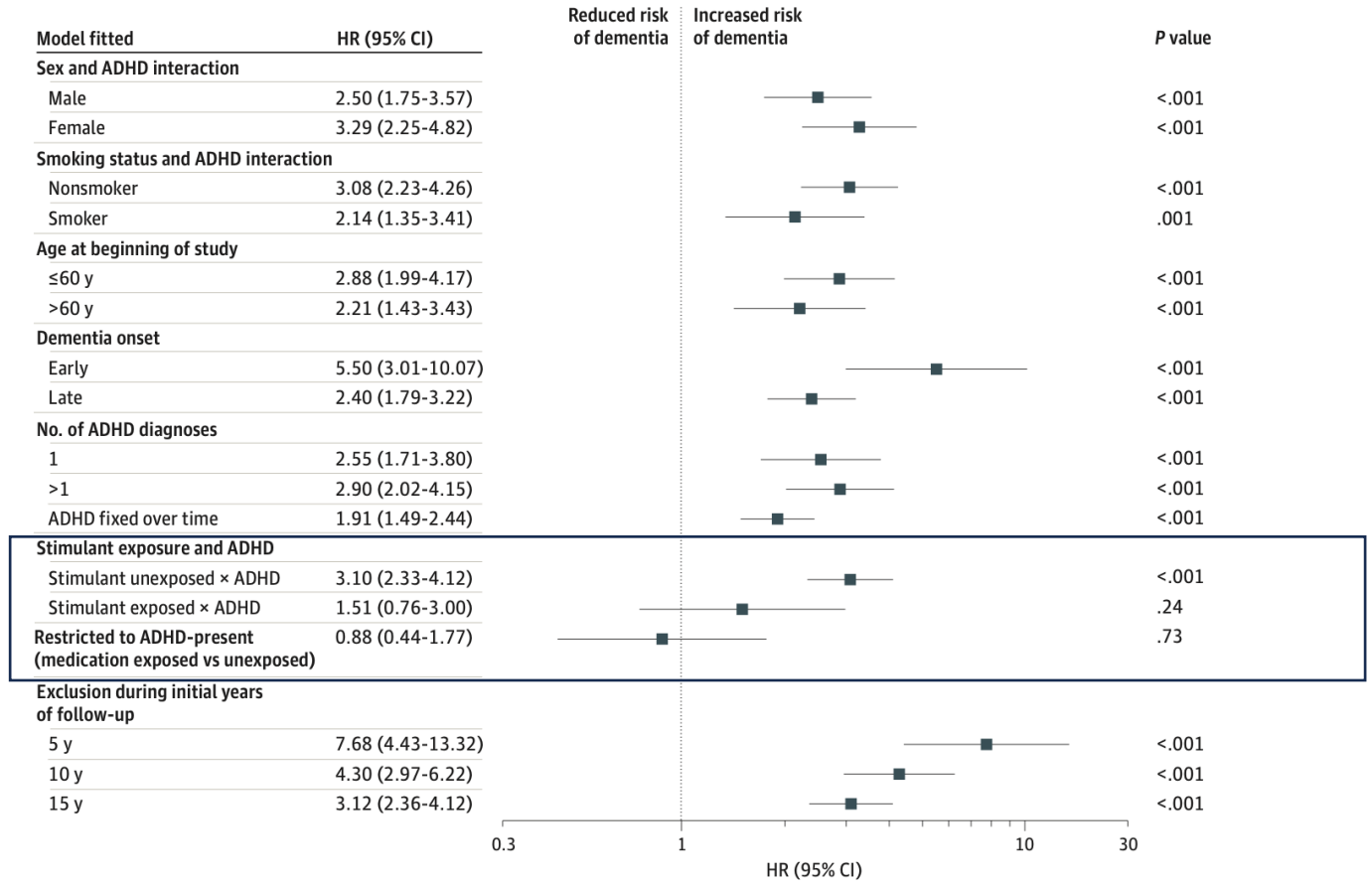
OBJECTIVE To exan

DESIGN, SETTING, A
109 218 members of
1952 who entered th
followed up to Febru
was conducted from

EXPOSURE Adult A
diagnosis (using the
Statistical Classificati

MAIN OUTCOME AN

Figure 3. Complementary Analysis of the Association Between Attention-Deficit/Hyperactivity Disorder (ADHD) and the Risk of Dementia



Model fitted	HR (95% CI)	*P* value
Sex and ADHD interaction		
Male	2.50 (1.75-3.57)	<.001
Female	3.29 (2.25-4.82)	<.001
Smoking status and ADHD interaction		
Nonsmoker	3.08 (2.23-4.26)	<.001
Smoker	2.14 (1.35-3.41)	.001
Age at beginning of study		
≤60 y	2.88 (1.99-4.17)	<.001
>60 y	2.21 (1.43-3.43)	<.001
Dementia onset		
Early	5.50 (3.01-10.07)	<.001
Late	2.40 (1.79-3.22)	<.001
No. of ADHD diagnoses		
1	2.55 (1.71-3.80)	<.001
>1	2.90 (2.02-4.15)	<.001
ADHD fixed over time	1.91 (1.49-2.44)	<.001
Stimulant exposure and ADHD		
Stimulant unexposed × ADHD	3.10 (2.33-4.12)	<.001
Stimulant exposed × ADHD	1.51 (0.76-3.00)	.24
Restricted to ADHD-present (medication exposed vs unexposed)	0.88 (0.44-1.77)	.73
Exclusion during initial years of follow-up		
5 y	7.68 (4.43-13.32)	<.001
10 y	4.30 (2.97-6.22)	<.001
15 y	3.12 (2.36-4.12)	<.001

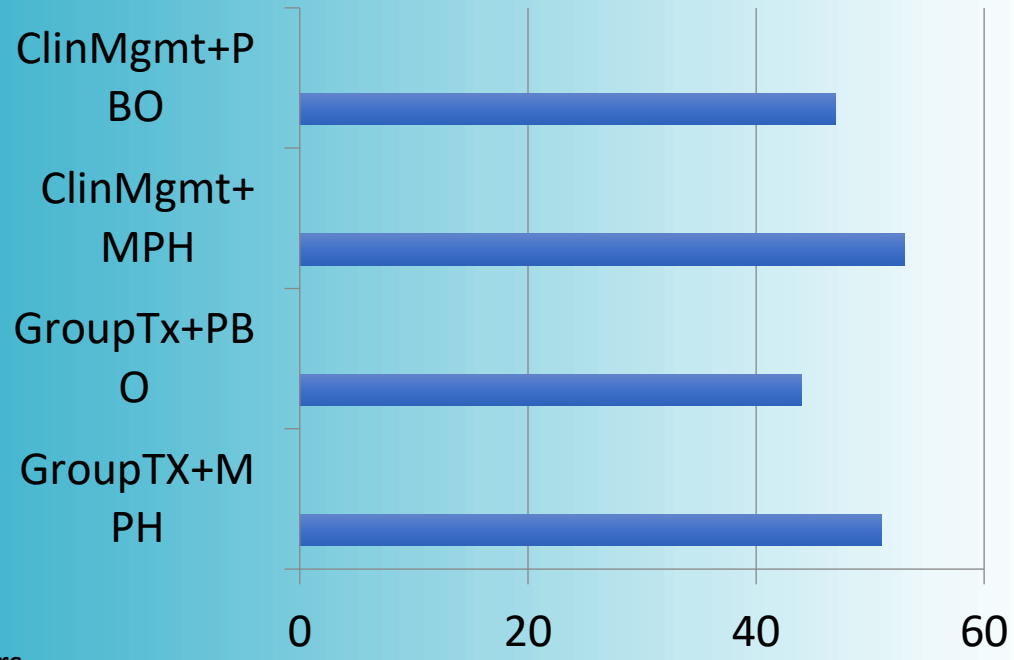
HR indicates hazard ratio from the Cox proportional hazards regression model. 95% CIs are Wald 2-sided 95% CIs. *P* values are for test of the hypothesis HR = 1 vs the hypothesis HR ≠ 1.

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 > J Clin Psychiatry. 2023 Oct 9;84(6):23m14934.
doi: 10.4088/JCP.23m14934.

Solriamfetol for Attention-Deficit/Hyperactivity Disorder in Adults: A Double-Blind Placebo-Controlled Pilot Study

Craig B H Surman [1,2], Daniel M Walsh [1], Nora Horick [1], Maura DiSalvo [1], Chloe Hutt Vater [1], Daniel Kaufman [1]

Affiliations + expand

PMID: 37819836 DOI: 10.4088/JCP.23m14934

Abstract

Objective: Some individuals with attention-deficit/hyperactivity disorder (ADHD) may not tolerate or adequately respond to currently available treatments. This study examined whether solriamfetol could have a favorable pattern of effects and tolerability as a treatment for ADHD in adults.

Methods: Sixty adults with *DSM-5* ADHD participated from August 2021 through January 2023 in a remotely conducted, randomized, double-blind, placebo-controlled, 6-week dose-optimization trial of 75 mg or 150 mg of solriamfetol. Measures included the Adult ADHD Investigator Symptom Rating Scale (AISRS), which was our primary outcome measure, as well as the Clinical Global Impressions scale (CGI), vital signs, the Global Assessment of Functioning (GAF), the Behavior Rating Inventory of Executive Function-Adult Form (BRIEF-A), the Epworth Sleepiness Scale (ESS), the Pittsburgh Sleep Quality Index (PSQI), and a modified Adult ADHD Self-Report Scale (MASRS).

Results: Solriamfetol was well tolerated, with no significant effect on mean heart rate (+3.7 vs +2.2 bpm, $P = .5609$), systolic blood pressure (+2.4 vs +1.5 mm Hg, $P = .6474$), or diastolic blood pressure (+1.1 vs +1.5 mm Hg, $P = .8117$). There was no statistically significant treatment effect on occurrence of adverse events. Compared to individuals on placebo, individuals on solriamfetol treatment experienced adverse events at a rate of at least 10 percentage points higher in the categories of decreased appetite, headache, gastrointestinal, insomnia, increased energy, cardiovascular, and neurologic. Compared to individuals on placebo, by study endpoint, a greater proportion of individuals in the treatment group met the a priori-defined treatment response (CGI score indicating much or very much improved and AISRS score reduced ≥ 25%: 45% vs 6.9%, $P = .0020$); those treated with solriamfetol also had greater improvement in total AISRS scores by week 3 through week 6 ($P = .0012$; week 6 effect size = 1.09). Significantly more solriamfetol-treated adults than placebo-treated adults had 0.5-standard deviation improvement in T-score on the BRIEF-A Global Executive Composite ($P = .0173$); those treated with solriamfetol also had greater mean change in GAF score (-4.8 vs -0.3, $P = .0006$) and greater mean MASRS total score change ($P = .0047$; effect size = 1.23). Mean ESS score improved more with solriamfetol than with placebo ($P = .0056$), but this difference did not predict AISRS response ($P = .3735$). There was no significant association between solriamfetol and change in PSQI scores.

Conclusions: Solriamfetol may be a novel and effective treatment for the management of ADHD in adults. Further replication in larger trials is indicated.

MASSACHUSETTS GENERAL HOSPITAL
PSYCHIATRY ACADEMY

Study of sleep agent in ADHD
N=60 adults
6 Week Study; 75 or 150 mg

Findings vs Placebo:
Response rate 45% vs 7% (p0.002)
Effect Size 1.1
Improved Executive Functioning
Good tolerability-no effect on CV or sleep

Multisite RCT underway
Not FDA approved for ADHD

ORIGINAL CONTRIBUTIONS

Efficacy, Safety, and Tolerability of Centanafadine Sustained-Release Tablets in Adults With Attention-Deficit/Hyperactivity Disorder

Results of 2 Phase 3, Randomized, Double-blind, Multicenter, Placebo-Controlled Trials

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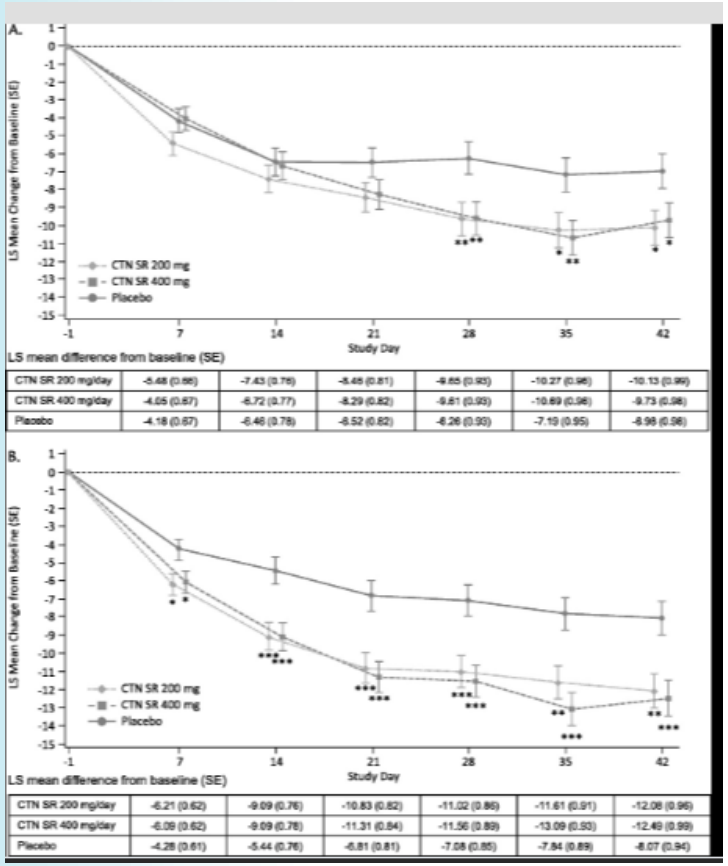

- 2 6 week, RCTs in Adults w ADHD (N= 876)
-Single blind run-in
-Dose 200 mg / day; or 200 mg /d x 1 week, then 400 mg/day
- Study 1 (CTN 200 mg/d, n = 149; CTN 400 mg/d, n = 149; placebo, n = 148) and study 2 (CTN 200 mg/d, n = 145; CTN 400 mg/d, n = 143; placebo, n = 142)
-ES (400 mg) 0.24, 0.4
-Side effects: GI, appetite decrease, psych

Not FDA approved

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

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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.

MASSACHUSETTS GENERAL HOSPITAL
PSYCHIATRY ACADEMY

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

Conclusions

- **ADHD in adults requires consideration of treatment**
- **Treatment with both stimulants and nonstimulants demonstrated both effective and safe**
- **Management requires baseline assessment; as well as ongoing reassessment and intervention**