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Long Term Functional Outcomes of ADHD: Impact of Pharmacotherapy

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Faculty Disclosure

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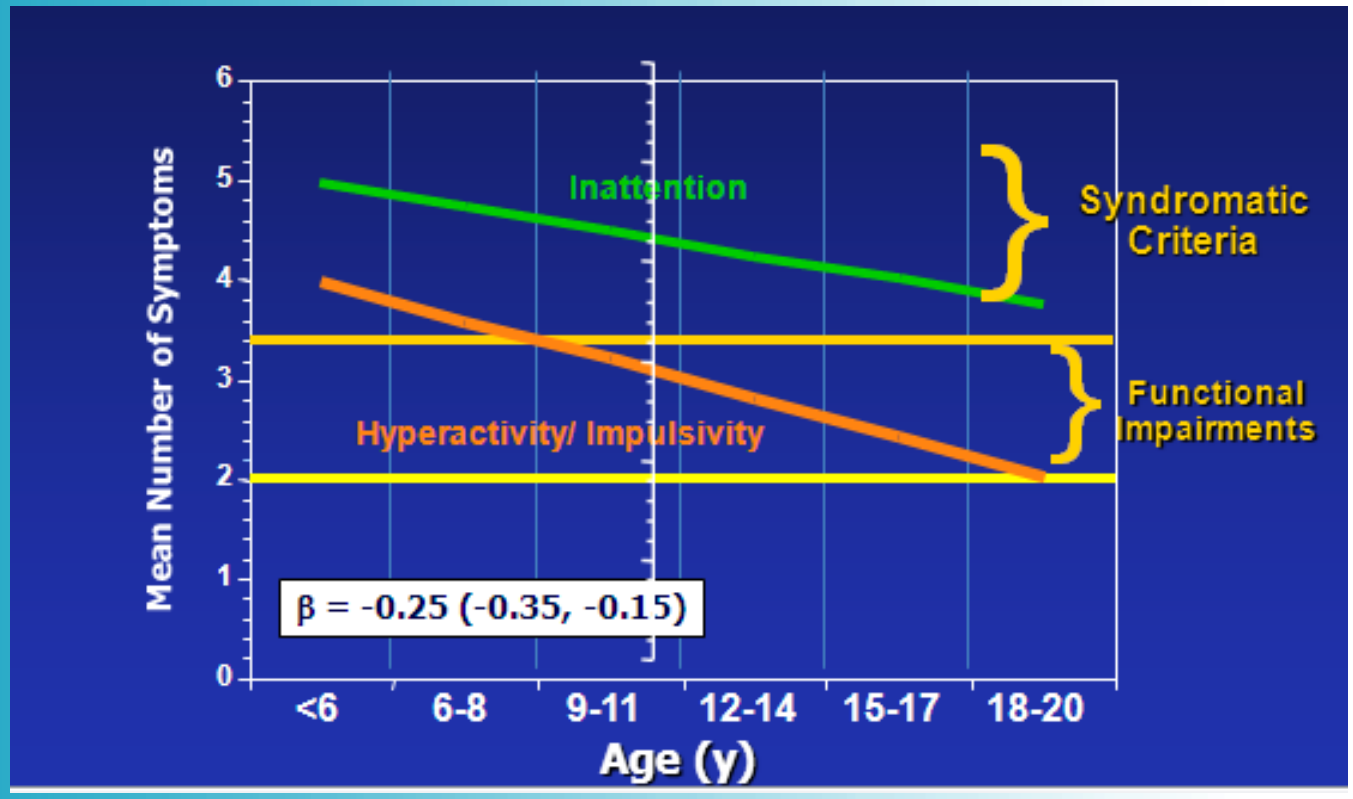
Timothy Wilens, MD has served as a consultant, or has received grant support from the following:

- NIH (NIDA), Food and Drug Administration
- Licensing agreement with 3D Therapeutics
- 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)

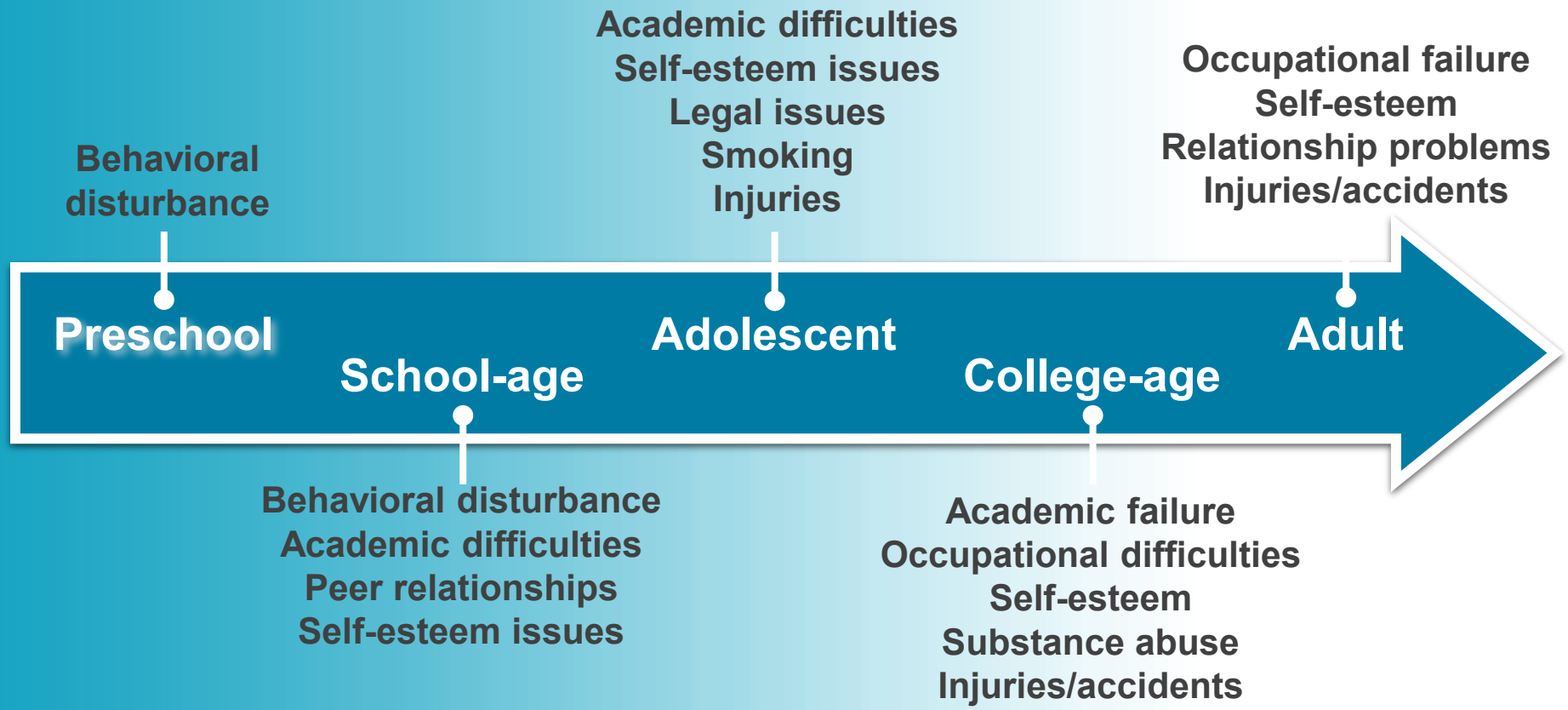
Some of the medications discussed may not be FDA approved in the manner in which they are discussed including diagnosis(es), combinations, age groups, dosing, or in context to other disorders (e.g., substance use disorders)

Age-Dependent Decline of ADHD Symptoms



Biederman J et al. *Am J Psychiatry*. 2000;157(5):816-818.

Developmental Impact of Untreated ADHD



Pliszka S. AACAP Work Group on Quality Issues. *J Am Acad Child Adolesc Psychiatry*. 2007;46(7):894-921.
Adler, Spencer, Wilens. ADHD in Children and Adults. 2015, Cambridge Press.

Medications: Attention-Deficit/ Hyperactivity Disorder

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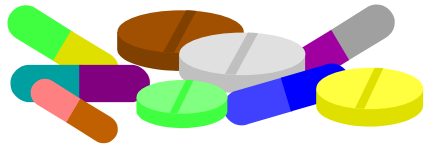

Pharmacological Treatment

- **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

Wilens TE, et al. *Postgrad Med*. 2010;122(5):97-109.
Newcorn & Wilens. *Child Adolesc Psych Clin N Am.* Elsevier Press 2022.

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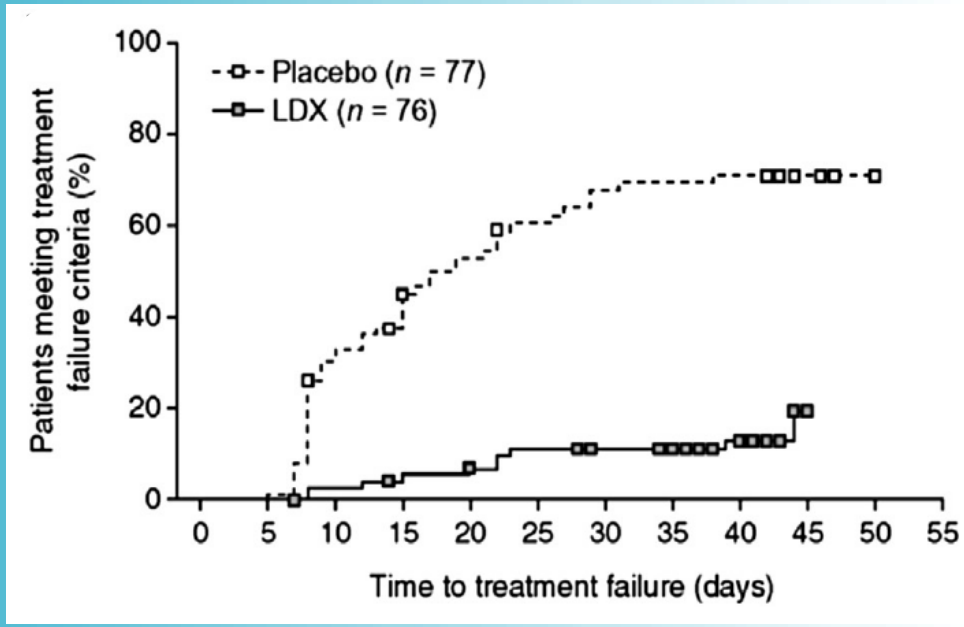
What Do We Know About Long-term Outcomes in Medication Treated ADHD Youth Growing Up?

Discontinuing Treatment Leads to ADHD Relapse



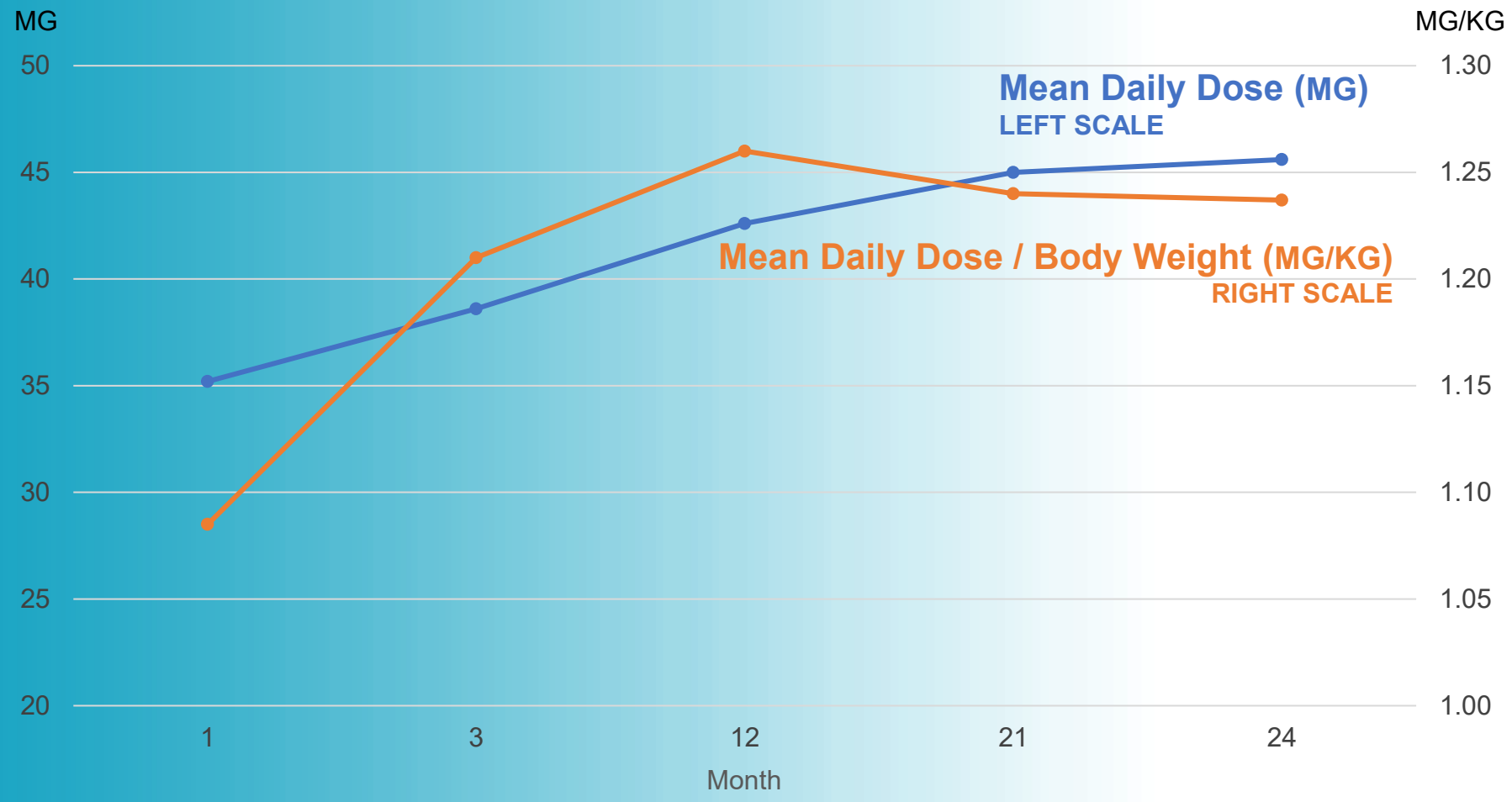
LDX = lisdexamfetamine

Treatment failure = 50% or greater increase in ADHD-RS-IV total score and a 2 point or greater increase in CGI-S score at any double-blind visit relative to start of randomized withdrawal period.

Coghill et al. *J Am Acad Child Adolesc Psychiatry.*2014;53(6):647-657.

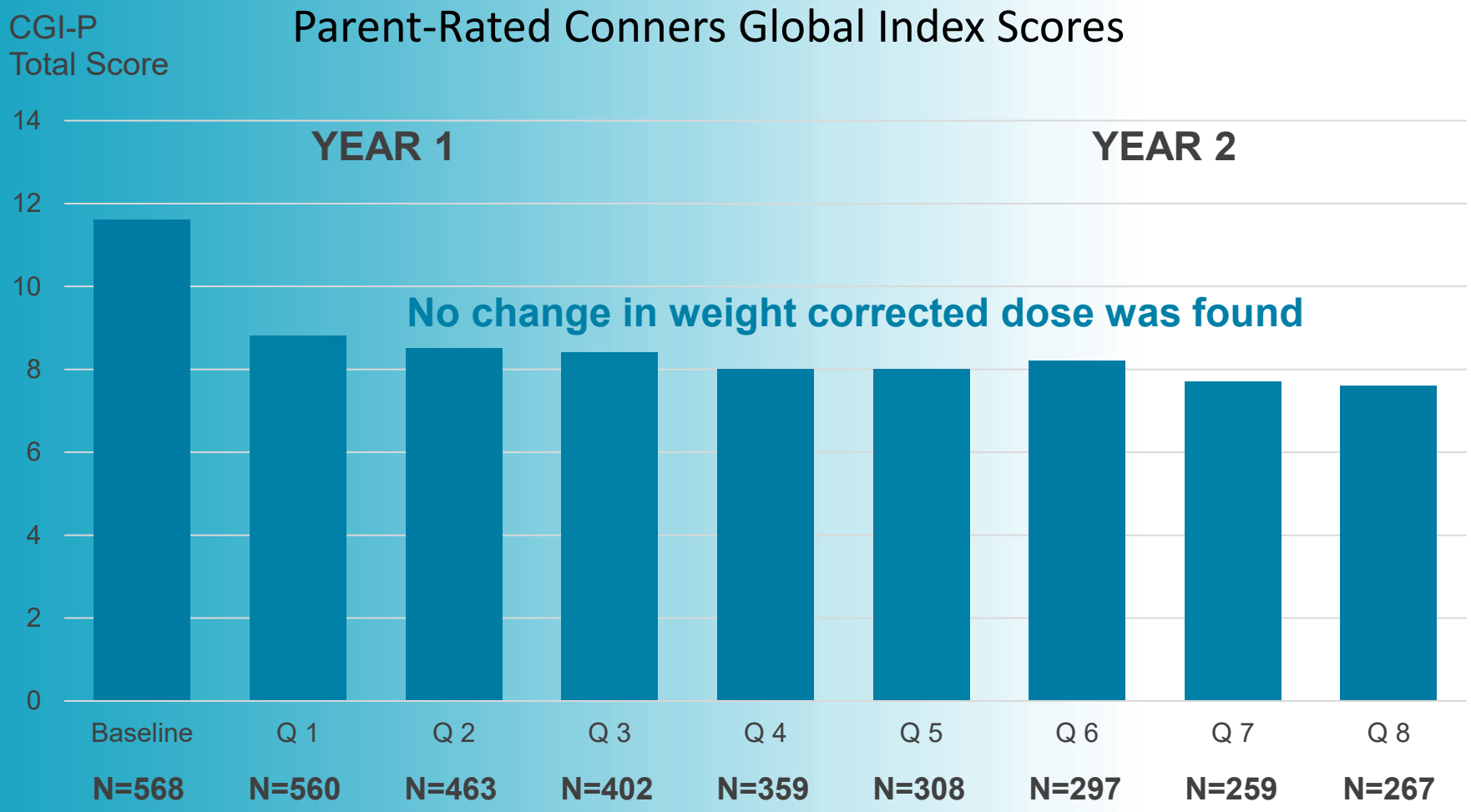
Dose of OROS® MPH (Concerta) Increases Over Two-Year Study

MTA: 26% increase in MPH dose by 14 months



Wilens et al. *JAACAP*: 2005

MAS XR Effectiveness



Mean Conners Global Index – Parent scores for ITT population.
Note: A lower CGI-P score indicates better response to treatment.

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It Takes Time to Show Long-term Outcomes: The Case of Juvenile-Onset Diabetes

- Wang et al. *Lancet*. 1993.
- Reichard et al. *N Engl J Med*. 1993.
- The Diabetes Control and Complications Group. *N Engl J Med*. 1993; and *Am J Cardiol*. 1995.

REVIEW ARTICLE

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Effect of Psychostimulants on Brain Structure and Function in ADHD: A Qualitative Literature Review of Magnetic Resonance Imaging–Based Neuroimaging Studies

Thomas J. Spencer, MD; Ariel Brown, PhD; Larry J. Seidman, PhD; Eve M. Valera, PhD; Nikos Makris, MD; Alexandra Lomedico, BA; Stephen V. Faraone, PhD; and Joseph Biederman, MD

Conclusions: Despite the inherent limitations and heterogeneity of the extant MRI literature, our review suggests that therapeutic oral doses of stimulants decrease alterations in brain structure and function in subjects with ADHD relative to unmedicated subjects and controls. These medication-associated brain effects parallel, and may underlie, the well-established clinical benefits.

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controlled studies that examined attention-deficit/hyperactivity disorder (ADHD) subjects on and off psychostimulants (as well as 5 relevant review articles).
Data Extraction: We combined details of study design and medication effects in each imaging modality.

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suggests that therapeutic oral doses of stimulants decrease alterations in brain structure and function in subjects with ADHD relative to unmedicated subjects and controls. These medication-associated brain effects parallel, and may underlie, the well-established clinical benefits.

Spencer TJ, et al. *J Clin Psychiatry*. 2013;74(9):902-917.

American College of Neuropsychopharmacology

www.nature.com/npp

ARTICLE

Stimulant medications in children with ADHD normalize the structure of brain regions associated with attention and reward

Feifei Wu[1,2,8], Wenchao Zhang[1,2,8], Weibin Ji[1,2], Yaqi Zhang[1,2], Fukun Jiang[1,2], Guanya Li[1,2], Yang Hu[1,2], Xiaorong Wei[3], Haoyi Wang[4], Szu-Yung (Ariel) Wang[5], Peter Manza[5], Dardo Tomasi[5], Nora D. Volkow[5], Xinbo Gao[6,7], Gene-Jack Wang[5]✉ and Yi Zhang[1,2]✉

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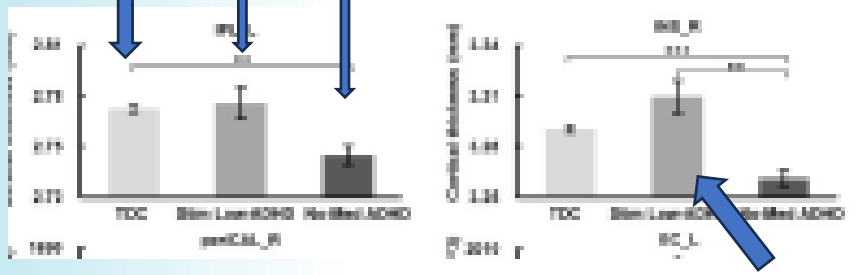
Children with ADHD show abnormal brain function and structure. Neuroimaging studies found that stimulant medications may improve brain structural abnormalities in children with ADHD. However, prior studies on this topic were conducted with relatively small sample sizes and wide age ranges and showed inconsistent results. In this cross-sectional study, we employed latent class analysis and linear mixed-effects models to estimate the impact of stimulant medications using demographic, clinical measures, and brain structure in a large and diverse sample of children aged 9-11 from the Adolescent Brain and Cognitive Development Study. We studied 273 children with low ADHD symptoms and received stimulant medication (Stim Low-ADHD), 1002 children with high ADHD symptoms and received no medications (No-Med ADHD), and 5378 typically developing controls (TDC). After controlling for the covariates, compared to Stim Low-ADHD and TDC, No-Med ADHD showed lower cortical thickness in the right insula (INS, $d = 0.340$, $P_{FDR} = 0.003$) and subcortical volume in the left nucleus accumbens (NAc, $d = 0.371$, $P_{FDR} = 0.003$), indicating that high ADHD symptoms were associated with structural abnormalities in these brain regions. In addition, there was no difference in brain structural measures between Stim Low-ADHD and TDC children, suggesting that the stimulant effects improved both ADHD symptoms and ADHD-associated brain structural abnormalities. These findings together suggested that children with ADHD appear to have structural abnormalities in brain regions associated with saliency and reward processing, and treatment with stimulant medications not only improve the ADHD symptoms but also normalized these brain structural abnormalities.

Neuropsychopharmacology; https://doi.org/10.1038/s41386-024-01831-4

Typically developing (non-ADHD; N=5378)

Treated ADHD (N=273)

Untreated ADHD (N=1002)



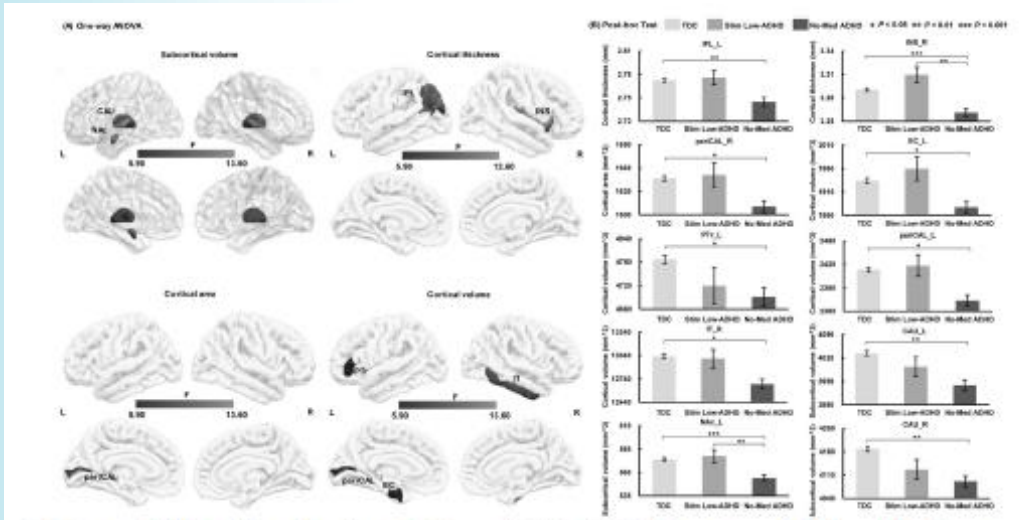


Fig. 2 One-way ANOVA analysis and post-hoc test. A One-way ANOVA analysis for brain structures. **B** Post-hoc test for brain structures. ADHD Attention-deficit/hyperactivity disorder, No-Med ADHD children with high ADHD symptoms and received no medications, Stim Low-ADHD children with low ADHD symptoms and received stimulant medication, TDC typically developing controls, L left hemisphere, R right hemisphere, IPL inferior parietal, INS insula, CUN cuneus, EC entorhinal cortex, PTr pars triangularis, periCAL pericalcarine, PCUN precuneus, IT inferior temporal, AMY Amygdala, CAU caudate, NAc nucleus accumbens.

ABCD Study
Cross sectional study
Aged 9-11 years

Wu et al., 2024; Neuropsychopharmacology; https://doi.org/10.1038/s41386-024-01831-4

ELSEVIER

Journal of Psychiatric Research

Volume 123, April 2020, Pages 21-30

A literature review and meta-analysis on the effects of ADHD medications on functional outcomes

Heidi Boland [a] ✉, Maura DiSalvo [a] ✉, Ronna Fried [a] ✉, K. Yvonne Woodworth [a] ✉, Timothy Wilens [b] ✉, Stephen V. Faraone [c] ✉, Joseph Biederman [b] ✉

Long-Term Studies of ADHD

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Stimulant Treated (Tx) vs. Untreated (UnTx) and Subsequent Mood Disorders

Study	Country	Total: N	ADHD: N	Age	Main Findings Tx vs. UnTx
Chang et al. 2016	Sweden	Not specified	38,752	8 – 46 yrs	Depression ↓
Lee et al. 2016	Taiwan	150,655	71,080	Mean 9.5 yrs	Depression ↓
Wang et al. 2016	Taiwan	22,800,000	144,920	All ages	Bipolar ↓
Jerrell et al. 2015	US	Not specified	22,452	Mean 7.8 yrs	Depression ↓

Boland et al. *Psychiatric Research*. 2020.

Long-Term Studies of ADHD

Stimulant Treated vs. Untreated and Subsequent Suicidality

Study	Country	Total: N	ADHD: N	Age	Main Findings Tx vs. UnTx
Liang et al 2018	Taiwan	Not specified	84,898	≤18 yrs	↓
Man et al 2017	China	Not specified	25,629	7 – 19 yrs	↓
Chen et al 2014*	Sweden	Not specified	37,936	13 – 28 yrs	↓

*Included nonstimulants (nonstimulants did not reduce suicide risk)
Boland et al. *Psychiatric Research*. 2020.

Long-Term Studies of ADHD

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Periods On versus Off Stimulant Medication and Criminality

Study	Country	Total: N	ADHD: N	Age	Main Findings Tx vs. UnTx
Mohr-Jensen et al 2019	Denmark	23,826	4,231	15 – 34 yrs	↓
Lichtenstein et al. 2012*	Sweden		25,656	≥ 15 yrs	↓

*Included nonstimulants
Boland et al. *Psychiatric Research*. 2020.

Medication for ADHD Reduces Criminality

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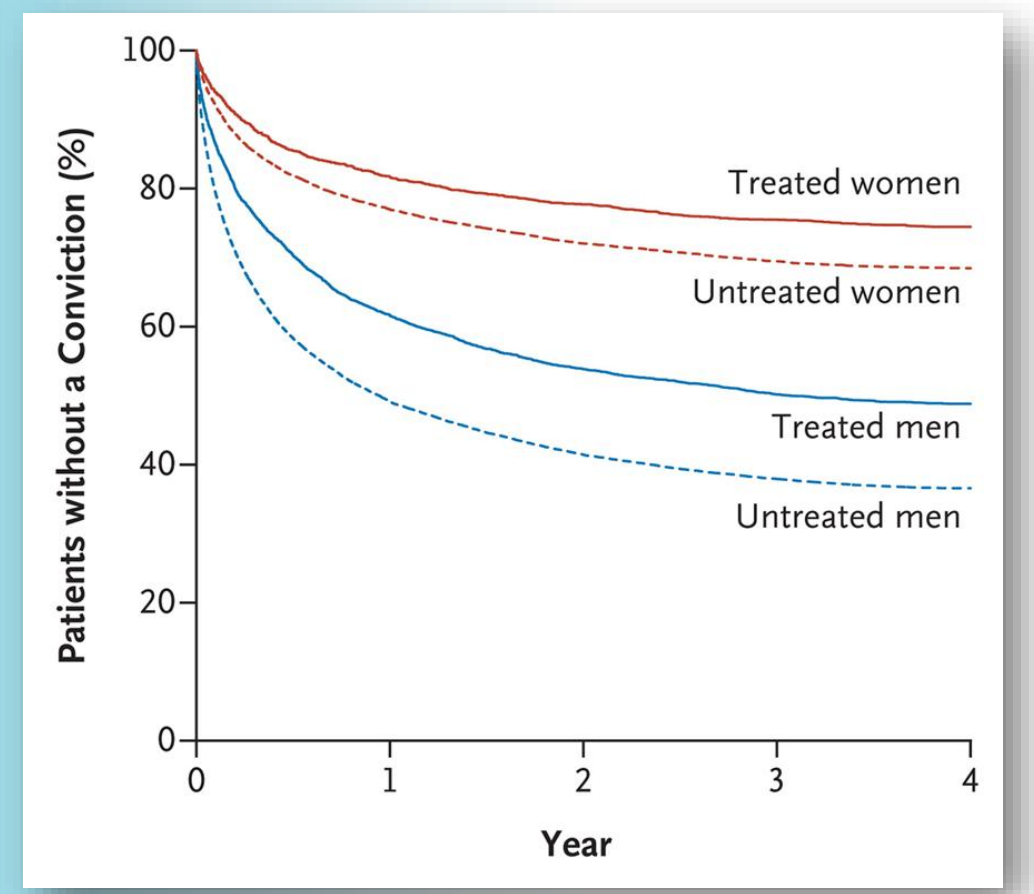
Swedish national registers
N=25,656 with ADHD, about 50% on medications

40% of convictions related to drug offenses (Tx OR=0.6).
No difference in type of ADHD medication (stimulants, nonstimulants) or level of crime.



Lichtenstein P et al. *N Engl J Med*. 2012;367(21):2006-2014.

Long-Term Studies of ADHD

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Stimulant Treated vs. Untreated and Subsequent Substance Use Disorders

Study	Country	Total: N	ADHD: N	Age	Main Findings Tx vs. UnTx
Quinn et al. 2017	USA	146,000,000	2,993,887	15 – 42 yrs	Within group ↓
Sundquist et al. 2015	Sweden	551,164	9,424	Mean 15 yrs	Between group ↔
Chang et al. 2014	Sweden		38,753	8 – 46 yrs	Between group ↓
Steinhausen et al. 2014	Denmark		20,742	11 – 20 yrs	Between & Within groups ↓

Boland et al. *Psychiatric Research*. 2020.

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Stimulant Treated vs. Untreated and Subsequent Traumatic Brain Injury

Study	Country	Total: N	ADHD: N	Age	Main Findings Tx vs. UnTx
Liao et al 2018	Taiwan		124, 438	≤18 yrs	↓
Liao et al 2018*	Taiwan		72,181	3 – 29 yrs	↓

*Included atomoxetine
Boland et al. *Psychiatric Research*. 2020.

Long-Term Studies of ADHD

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Periods On vs. Off Stimulant Medication and Motor Vehicle Accidents

Study	Country	Total: N	ADHD: N	Age	Main Findings Tx vs. UnTx
Chang et al 2017*	USA		2,319,450	Mean 32.5 yrs	
Chang et al 2014*	Sweden		17,408	18 – 46 yrs	

*Included atomoxetine
Boland et al. *Psychiatric Research*. 2020.

Long-Term Studies of ADHD

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Stimulant Treated vs. Untreated and Academic Achievement

Study	Country	Total: N	ADHD: N	Age	Findings: Tx vs. UnTx
Jangmo et al. 2019	Sweden	657,720	29,128		GPA ↑
Kellow et al. 2018*	Denmark	577,551	6,444	Mean 16.1 yrs	GPA ↑
Lu et al. 2017*	Sweden	61,640	3,718	Mean 22 yrs	Entrance Exams ↑
Marcus et al. 2011	USA		3,543		GPA ↑
Barberesi et al. 2007	USA	5,718	370	Mean 18.4 yrs	Reading Attendance ↑
Currie et al. 2014	Canada			< 16 yrs	Academic Outcomes ↔
Zoega et al. 2012	Iceland	13,617	1,029	9 – 12 yrs	Test scores ↓
Van der Schans 2017	Netherlands	600,000	7,736	12-13 yrs	School Performance ↓

*Included nonstimulants

Boland et al. *Psychiatric Research*. 2020.

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ADHD drug treatment and risk of suicidal behaviours, substance misuse, accidental injuries, transport accidents, and criminality: emulation of target trials

Le Zhang,[1] Nanbo Zhu,[2] Arvid Sjölander,[1] Mikail Nourredine,[3,4,5] Lin Li,[1] Miguel Garcia-Argibay,[1,3,6,7] Ralf Kuja-Halkola,[1] Isabell Brikell,[1,8,9] Paul Lichtenstein,[1] Brian M D'Onofrio,[1,10] Henrik Larsson,[1,3,6] Samuele Cortese,[3,11,12,13,14] Zheng Chang[1]

For numbered affiliations see end of the article

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Additional material is published online only. To view please visit the journal online.

Cite this as: *BMJ* 2025;390:e083658
http://dx.doi.org/10.1136/bmj-2024-083658

Accepted: 11 June 2025

ABSTRACT

OBJECTIVE

To examine the effects of drug treatment for attention deficit/hyperactivity disorder (ADHD) on suicidal behaviours, substance misuse, accidental injuries, transport accidents, and criminality.

DESIGN

Emulation of target trials.

SETTING

Linkage of national registers in Sweden, 2007-20.

PARTICIPANTS

People aged 6-64 years with a new diagnosis of ADHD, who either started or did not start drug treatment for ADHD within three months of diagnosis.

MAIN OUTCOME MEASURES

First and recurrent events of five outcomes over two years after ADHD diagnosis: suicidal behaviours, substance misuse, accidental injuries, transport accidents, and criminality.

RESULTS

Of 148 581 individuals with ADHD (median age 17.4 years; 41.3% female), 84 282 (56.7%) started drug treatment for ADHD, with methylphenidate being the most commonly prescribed at initiation (74 515; 88.4%). Drug treatment for ADHD was associated with reduced rates of the first occurrence of suicidal behaviours (weighted incidence rates 14.5 per 1000 person years in the initiation group versus 16.9 in the non-initiation group; adjusted incidence rate ratio 0.83, 95% confidence interval 0.78 to 0.88), substance misuse (58.7 *v* 69.1 per 1000 person years; 0.85, 0.83 to 0.87), transport accidents (24.0 *v* 27.5 per 1000 person years; 0.88, 0.82 to 0.94), and criminality (65.1 *v* 76.1 per 1000 person years; 0.87, 0.83 to 0.90), whereas the reduction was not statistically significant for accidental injuries (88.5 *v* 90.1 per 1000 person years; incidence rate ratio 0.98, 0.96 to 1.01). The reduced rates were more pronounced among individuals with previous events, with incidence rate ratios ranging from 0.79 (0.72 to 0.86) for suicidal behaviours to 0.97 (0.93 to 1.00) for accidental injuries. For recurrent events, drug treatment for ADHD was significantly associated with reduced rates of all five outcomes, with incidence rate ratios of 0.85 (0.77 to 0.93) for suicidal behaviours, 0.75 (0.72 to 0.78) for substance misuse, 0.96 (0.92 to 0.99) for accidental injuries, 0.84 (0.76 to 0.91) for transport accidents, and 0.75 (0.71 to 0.79) for criminality.

CONCLUSIONS

Drug treatment for ADHD was associated with beneficial effects in reducing the risks of suicidal behaviours, substance misuse, transport accidents, and criminality but not accidental injuries when considering first event rate. The risk reductions were more pronounced for recurrent events, with reduced rates for all five outcomes. This target trial emulation study using national register data provides evidence that is representative of patients in routine clinical settings.

Med treatment of ADHD Results in Lower Incidence of Negative Outcomes

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Lower incidence

Initiation *v* non-initiation strategy	Initiation incidence rate	Non-initiation incidence rate	Incidence rate ratio (95% CI)
First events			
Suicidal behaviours	14.5	16.9	0.83 (0.78 to 0.88)
Substance misuse	58.7	69.1	0.85 (0.83 to 0.87)
Accidental injuries	88.5	90.1	0.98 (0.96 to 1.01)
Transport accidents	24.0	27.5	0.88 (0.82 to 0.94)
Criminality	65.1	76.1	0.87 (0.83 to 0.90)
Recurrent events			
Suicidal behaviours	22.7	24.3	0.85 (0.77 to 0.93)
Substance misuse	166.1	201.5	0.75 (0.72 to 0.78)
Accidental injuries	119.4	122.8	0.96 (0.92 to 0.99)
Transport accidents	31.6	37.2	0.84 (0.76 to 0.91)
Criminality	111.3	143.4	0.75 (0.71 to 0.79)

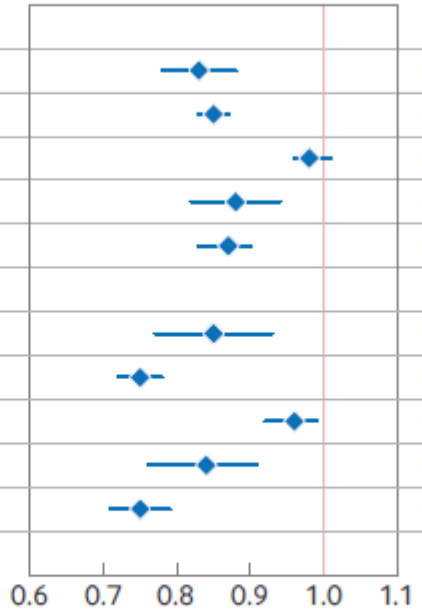

Fig 3 | Attention deficit/hyperactivity disorder (ADHD) drug treatment and rates of first and recurrent outcome events over two years of follow-up among people with ADHD. Incidence rates were calculated per 1000 person years. Numbers reported are weighted and account for follow-up censoring, including treatment discontinuation or switching. CI=confidence interval

Swedish registry study
Age 6 – 64 years with new diagnosis of ADHD
Started (initiation) vs did not start meds
2 years follow-up
N= 148 581 individuals with ADHD
Median age 17.4 years; 41.3% female
N= 84 282 (57%) who started meds for ADHD
--MPH most common at initiation (74, 515; 88%)

the bmj | BMJ 2025;390:e083658 | doi: 10.1136/bmj-2024-083658

Conclusions

- **ADHD is considered a lifespan disorder**
- **Consider the implications of not treating ADHD**
- **Long term treatment does not result in neurotoxicity; trends to structural and functional normalization**
- **Long term pharmacotherapy of ADHD, largely with stimulants, results in improvement in virtually all functional outcomes**
- **The impact of the timing of initiation, duration and adequacy of treatment on long term functional outcomes remains unclear**