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Long Term Functional Outcomes of ADHD: Impact of Pharmacotherapy

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Faculty Disclosure

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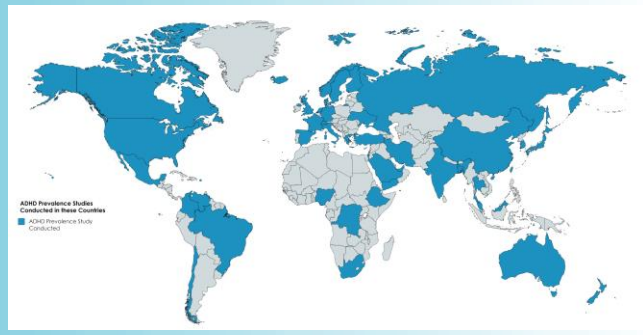
Timothy Wilens, MD has served as a consultant, or has received grant support from the following:

- NIH (NIDA), Food and Drug Administration, 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)

ADHD Overview



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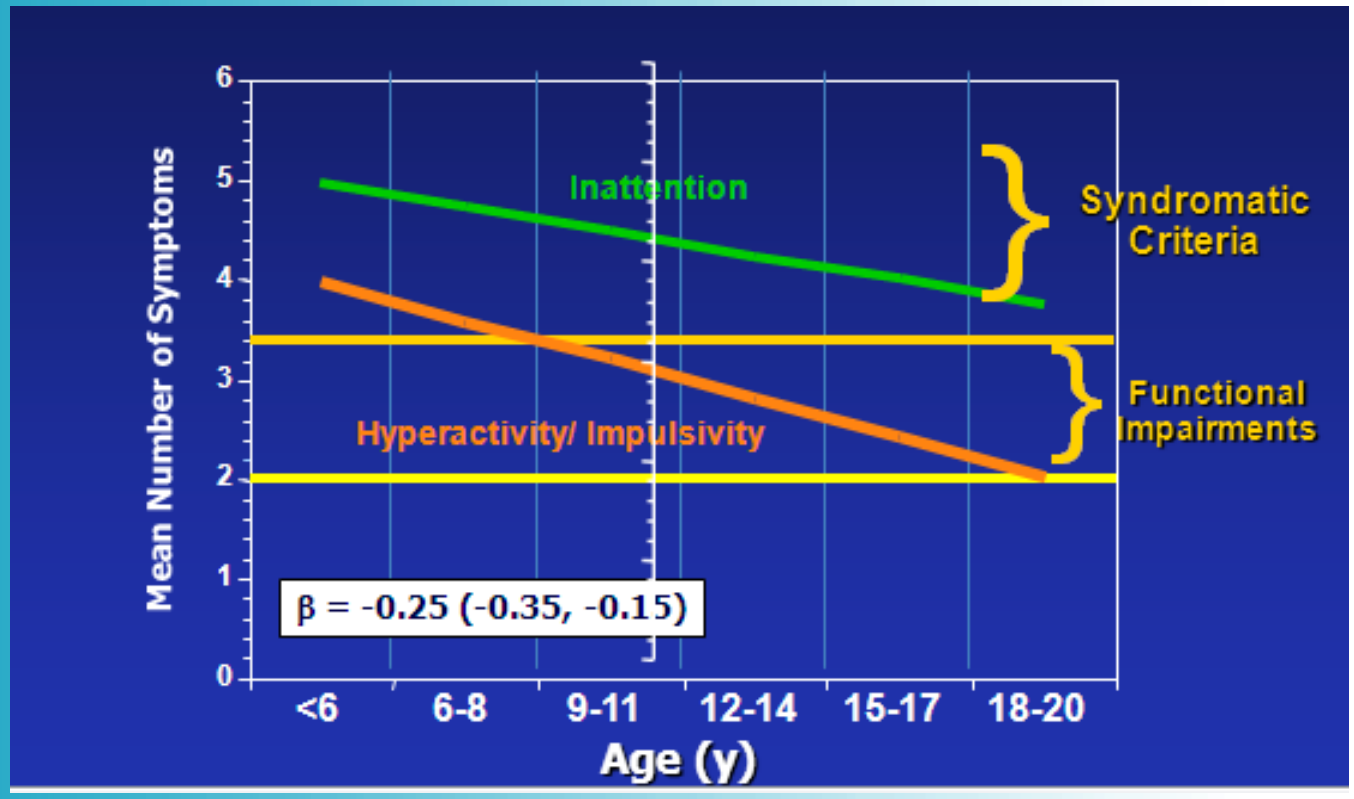
- **ADHD prevalence among 8- to 15-year-olds: 8.7%**
- **ADHD prevalence among 18- to 44-year-olds: 4.4%**
- **Associated with chronic course**
  - **Circa 75% persistence from childhood into adolescence**
  - **Circa 50% persistence from childhood into adulthood**

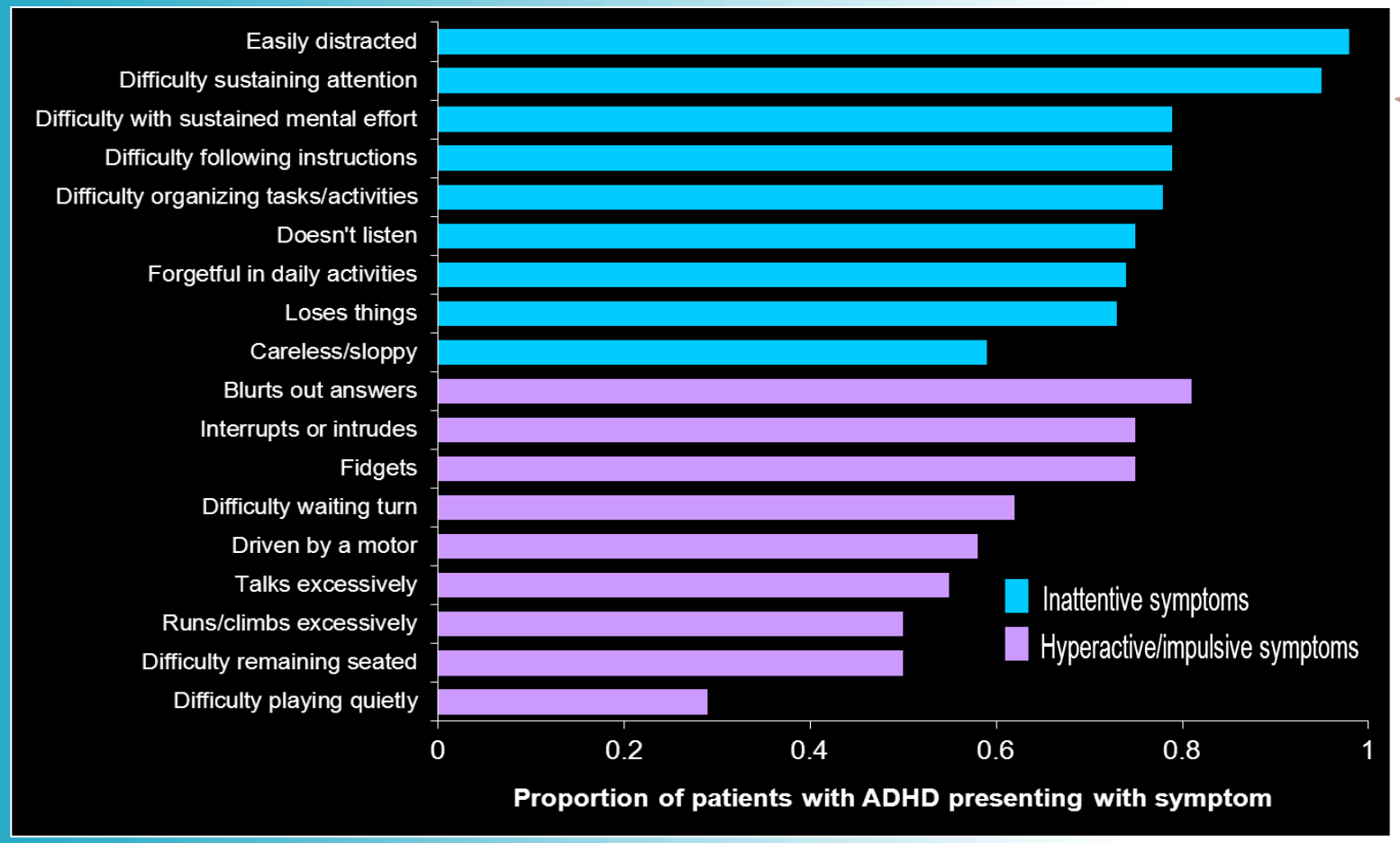
Froehlich TE, et al. *Arch Pediatr Adolesc Med*. 2007;161(9):857-864.
Kessler RC, et al. *Am J Psychiatry*. 2006;163(4):716-723.
Wilens TE, et al. *Postgrad Med*. 2010;122(5):97-109.
Faraone et al. *Nature Neuroscience*, 2015; 2021 International Consensus Statement on ADHD.

Age-Dependent Decline of ADHD Symptoms



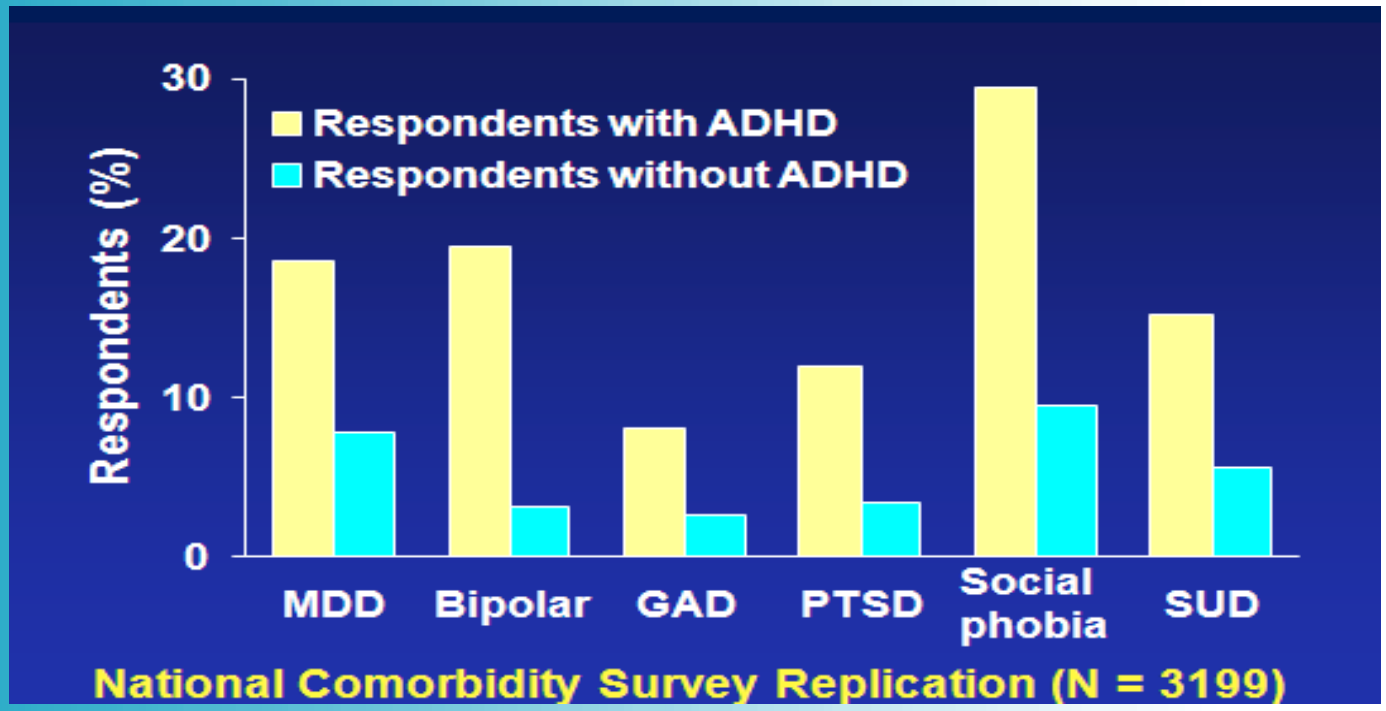
Biederman J et al. *Am J Psychiatry*. 2000;157(5):816-818.

Presenting Symptoms in Adults with ADHD



Wilens TE et al. *J Clin Psychiatry*. 2009;70(11):1557-1562.

ADHD Is Commonly Comorbid with Psychiatric Disorders (Epidemiological Sample)



Among respondents aged 18-44 years with ADHD, comorbid disorder within previous 12 months. For all comparisons, $P<0.05$.

Kessler RC et al. *Am J Psychiatry*. 2006;163(4):716-723.

Developmental Impact of Untreated ADHD

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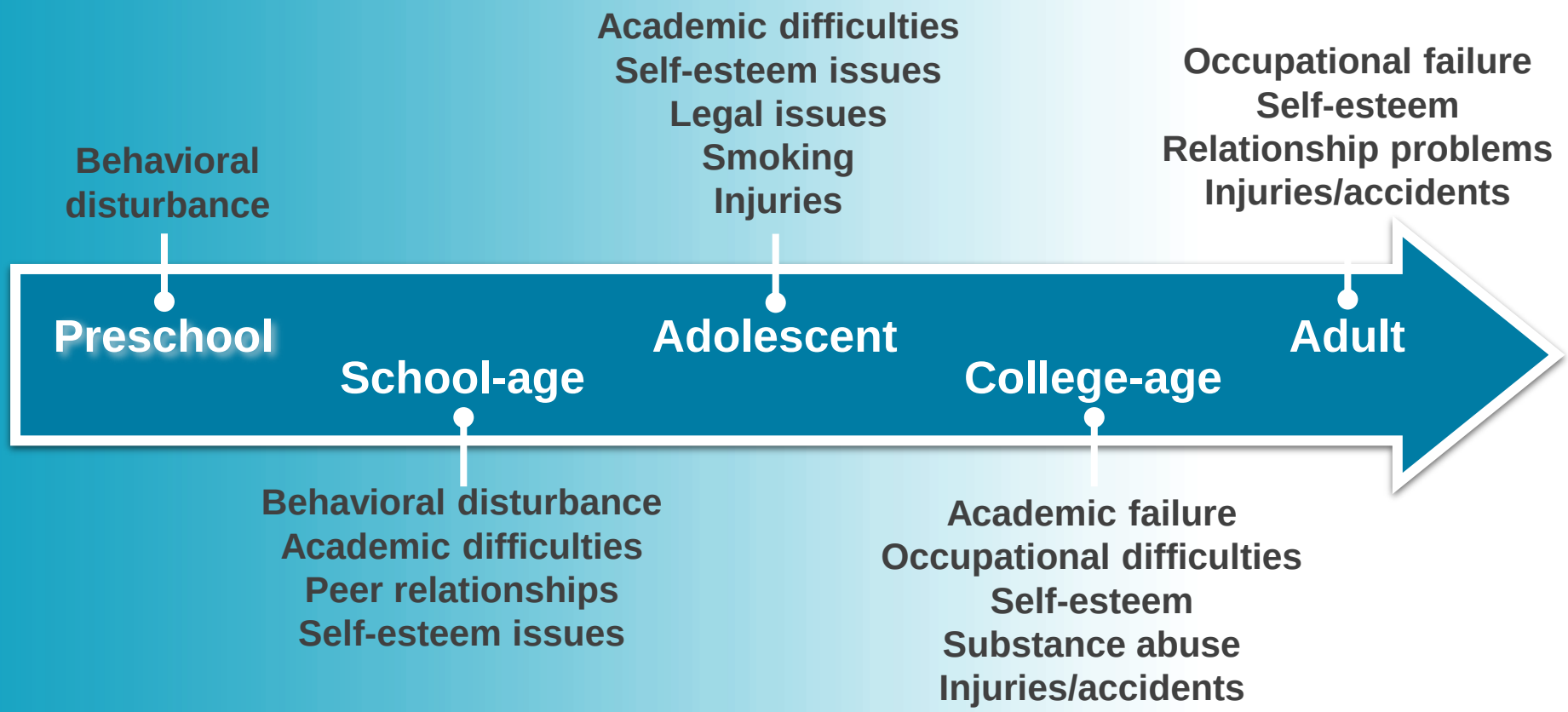

Pliszka S. AACAP Work Group on Quality Issues. *J Am Acad Child Adolesc Psychiatry*. 2007;46(7):894-921.
Adler, Spencer, Wilens. ADHD in Children and Adults. 2015, Cambridge Press.

Medications: Attention-Deficit/ Hyperactivity Disorder

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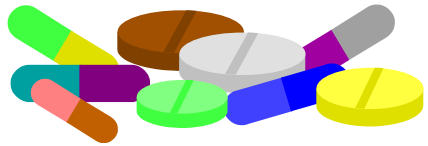

Pharmacological Treatment

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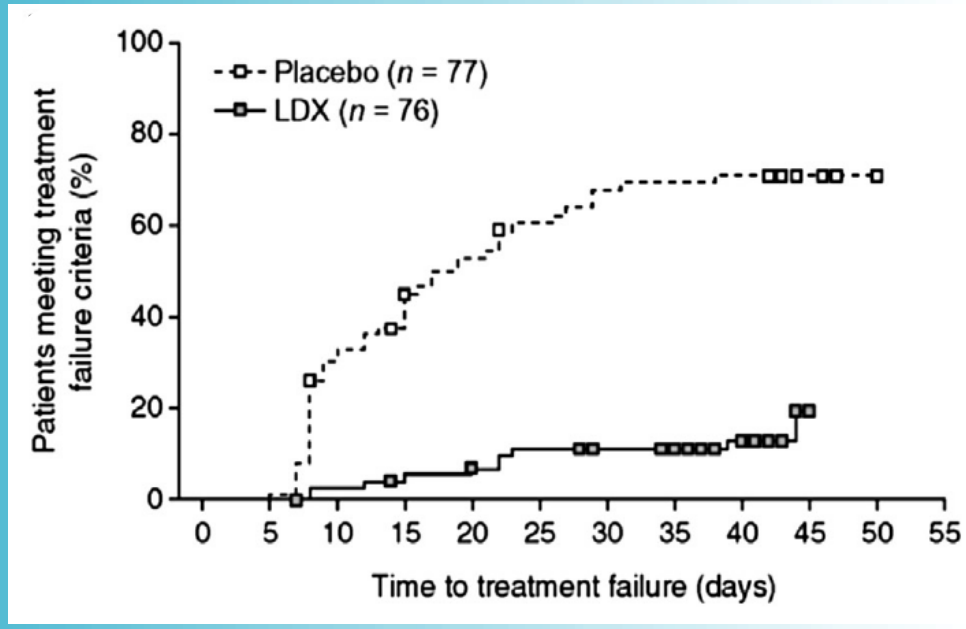
What Do We Know About Long-term Outcomes in Medication Treated ADHD Youth Growing Up?

Discontinuing Treatment Leads to ADHD Relapse

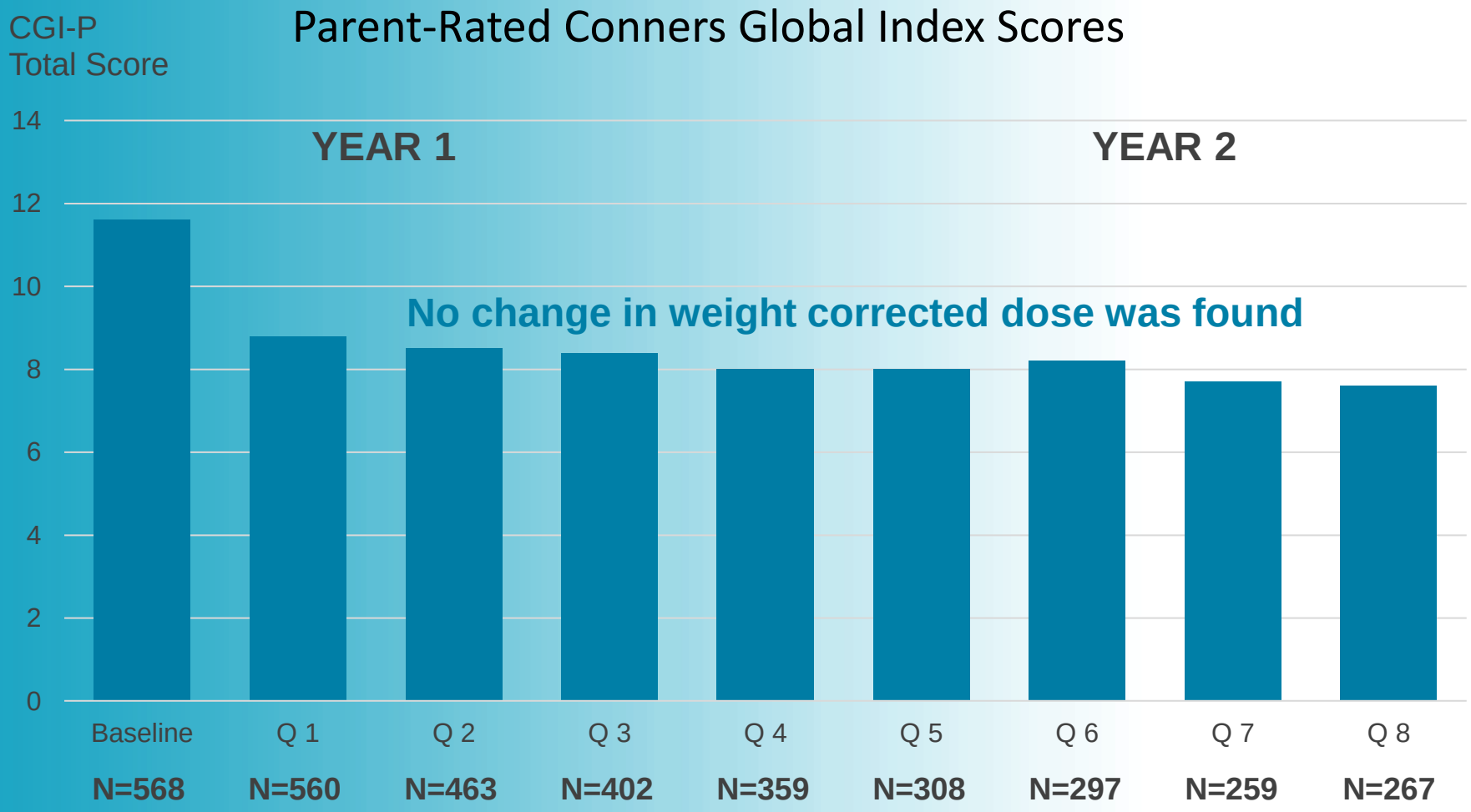


LDX = lisdexamfetamine

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.

MAS XR Effectiveness



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

What are the long-term effects of long-term treatment on a chronic disorder?

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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

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

Thomas J. Sp
Eve M. Valer
Stephen V. F

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.

ABSTRACT

Objective: To eva
doses of stimulan
measured by mag
neuroimaging stu
spectroscopy).

Data Sources: We
through the end
keywords (1) *psyc*
amphetamine, an
and (3) *ADHD* or *A*
disorder or *attenti*

Study Selection: We included only English language articles with new data from case-control or placebo 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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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.

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

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

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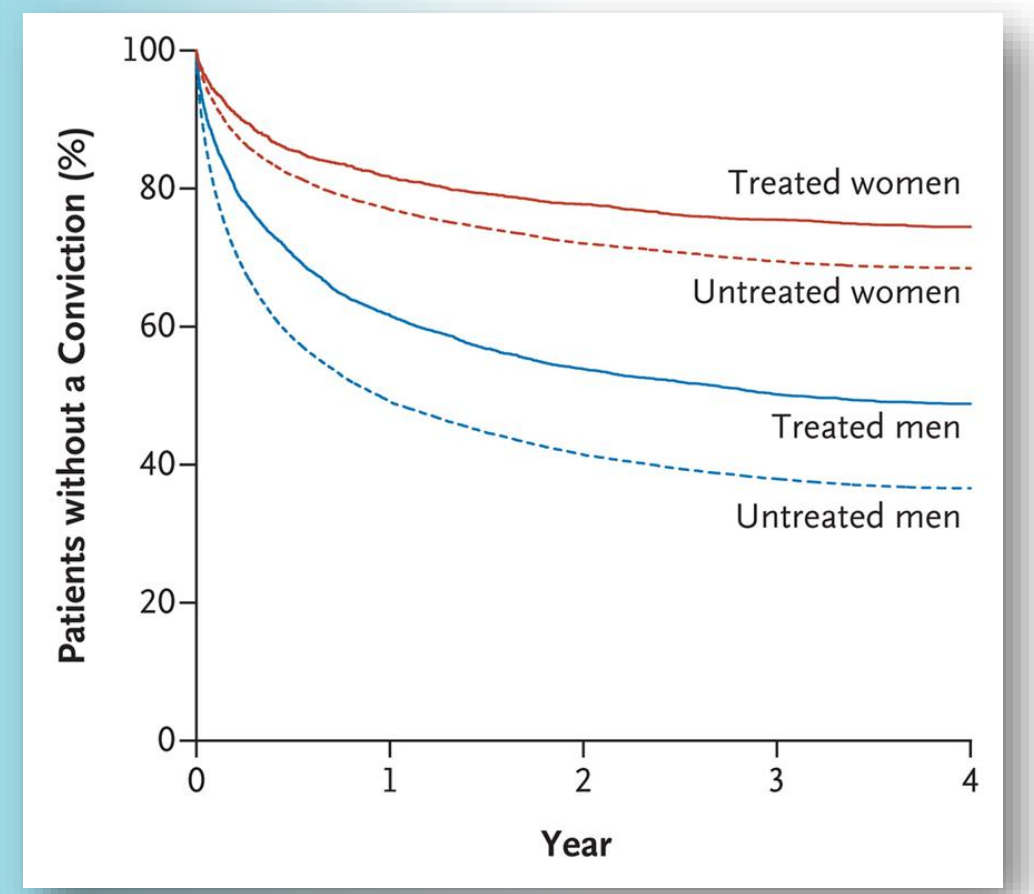
Swedish national registers
N=25,656 with ADHD, about 50% on medications

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.

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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.

Early ADHD Treatment Reduces Marijuana Use

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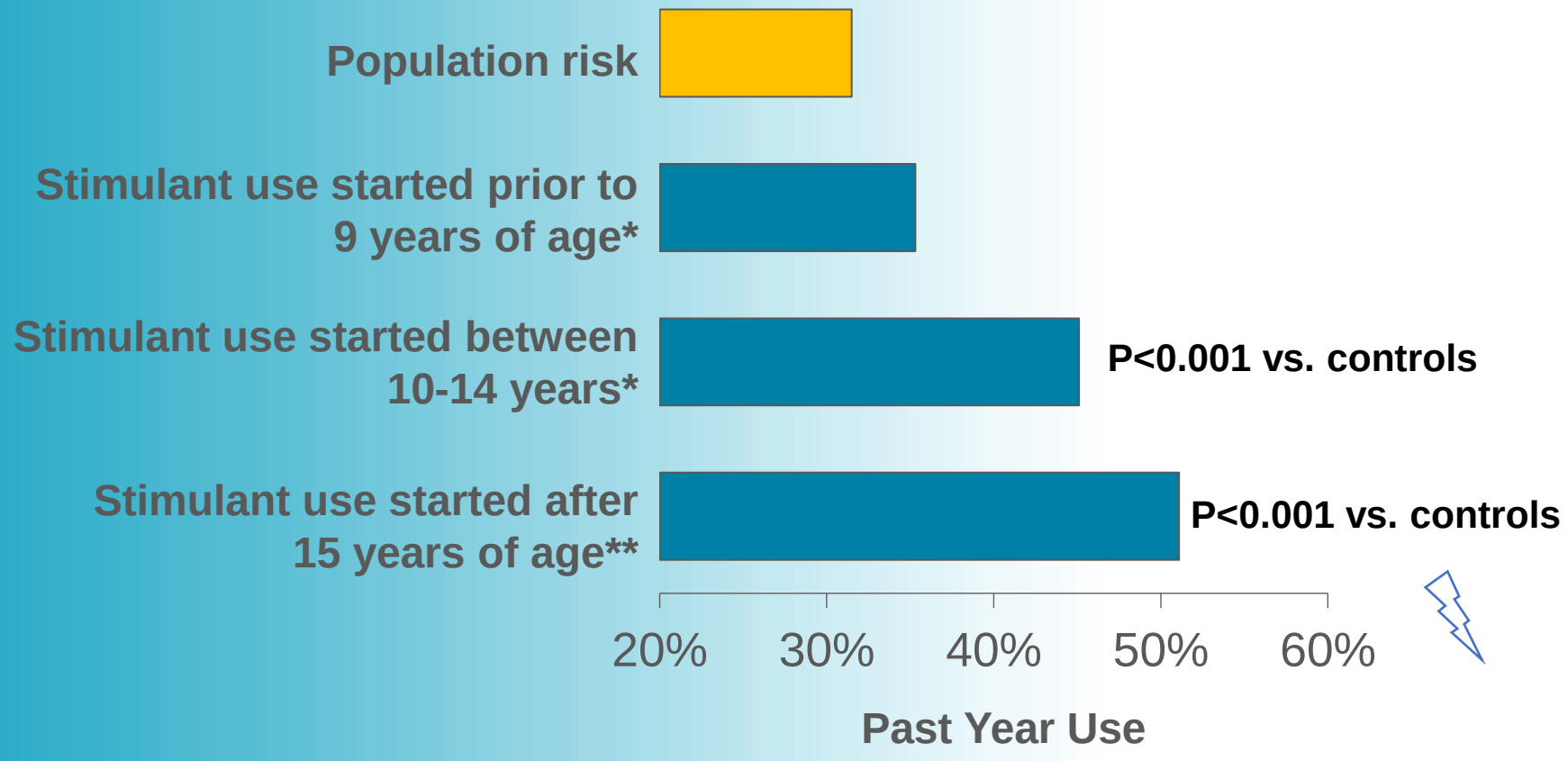
10 Cohorts of Senior Years 2005 to 2014

(N=40,358; ca. 10% with ADHD)



* > 6 years of treatment
** > 3 years of treatment

McCabe, West, Dickinson, Wilens. *J Am Acad Child Adoles Psych.* 2016:55:479-486.

Long-Term Studies of ADHD

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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.

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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.

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