Successfully treating ADHD and its comorbidities

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Faculty Disclosure

- **Dr. Mattingly**: Consultant—AbbVie, Acadia Pharmaceuticals, Alkermes, Inc., Axsome Therapeutics, Corium, Eisai, Ironshore Pharmaceuticals & Development, Inc., Intra-Cellular Therapies, Inc., Janssen Pharmaceuticals, Lundbeck, Neos Therapeutics, Inc., Neurocrine Biosciences, Otsuka Pharmaceutical, Redax, Roche Pharma, Rhodes Pharmaceuticals, Sage Therapeutics, Shire, Sunovion, Supernus Pharmaceuticals, Takeda Pharmaceutical, Teva Pharmaceuticals, Tris Pharma Inc.; Grant/Research Support—AbbVie, Acadia Pharmaceuticals, Alkermes, Inc., Avanir Pharmaceuticals Inc, Axsome Therapeutics, Boehringer Ingelheim, Emalex Biosciences, Janssen Pharmaceuticals, Medgenics, NLS-1 Pharma AG, Redax, Roche Pharma, Sage Therapeutics, Shire, Sunovion, Supernus Pharmaceuticals, Takeda Pharmaceutical, Teva Pharmaceuticals; Speakers Bureau—AbbVie, Alkermes, Inc., Corium, Eisai, Janssen Pharmaceuticals, Lundbeck, Neurocrine Biosciences, Otsuka Pharmaceutical, Sunovion, Supernus Pharmaceuticals, Takeda Pharmaceutical, Tris Pharma Inc.

- **Dr. Maletic**: Consultant—Acadia, Alkermes, Inc., Allergan, Eisai, Intra-Cellular, Lundbeck A/S, Otsuka America Pharmaceutical, Inc., Sunovion Pharmaceuticals Inc., Supernus Pharmaceuticals, Inc., Takeda Pharmaceutical Company Limited, Teva Pharmaceutical Industries Ltd.; Speakers Bureau—Alkermes, Inc., Allergan, Eisai, Intra-Cellular, Ironshore Pharmaceuticals, Lundbeck A/S, Otsuka America Pharmaceutical, Inc., Sunovion Pharmaceuticals Inc., Takeda Pharmaceutical Company Limited; Speakers Bureau (spouse)—Otsuka.

Disclosure

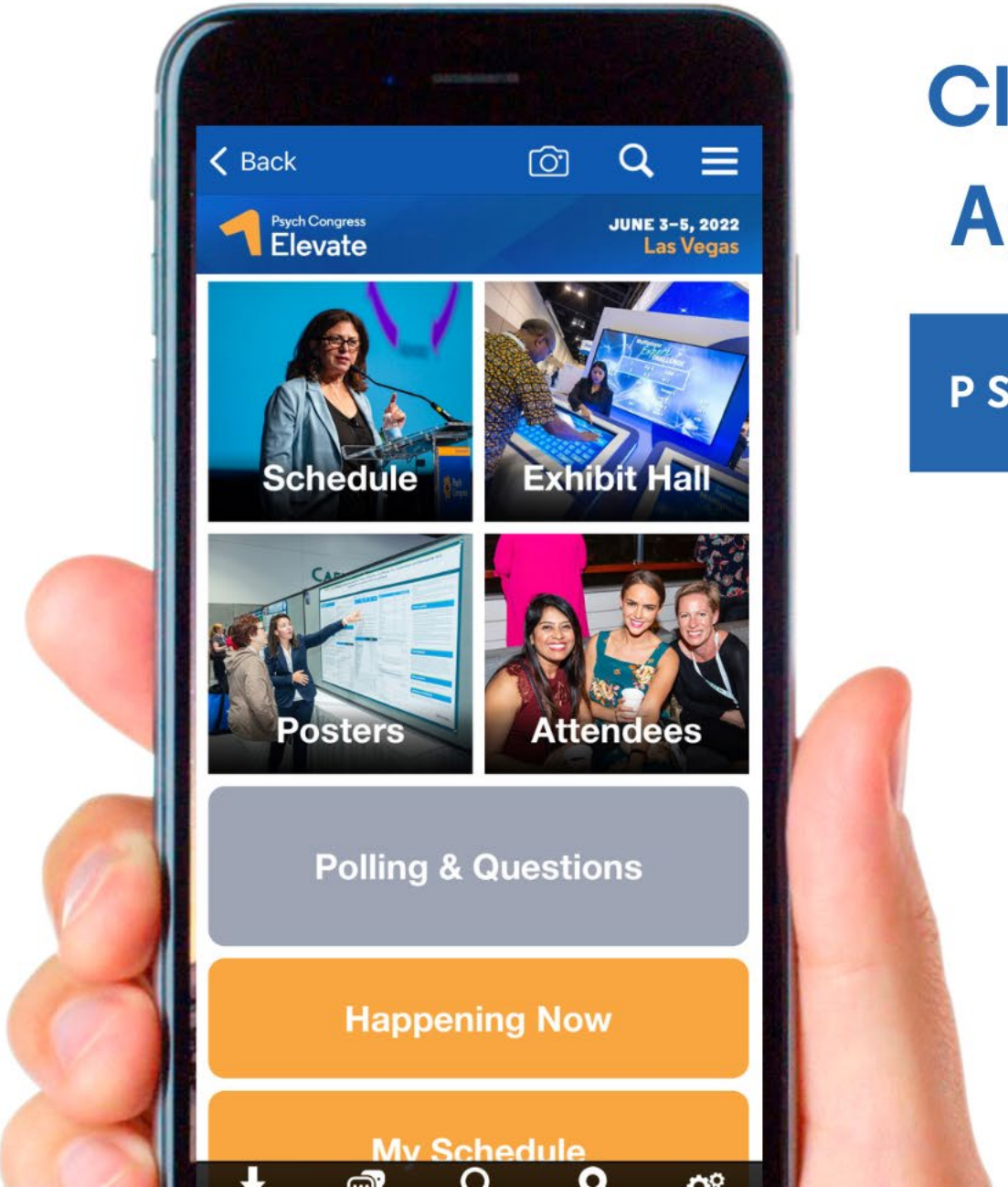
- The faculty have been informed of their responsibility to disclose to the audience if they will be discussing off-label or investigational use(s) of drugs, products, and/or devices (any use not approved by the US Food and Drug Administration).
- Applicable CME staff have no relationships to disclose relating to the subject matter of this activity.
- This activity has been independently reviewed for balance.

Learning Objectives

- Describe shared genetics and neurobiological underpinning of attention-deficit/hyperactivity disorder (ADHD) and its common comorbidities

- Discuss the diagnostic challenges and solutions for timely identification of ADHD and its comorbidities

- Review the best treatment strategies and emerging treatments for ADHD and its comorbidities



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PSYCHOPHARMACOLOGY (OCTAVIUS 11)

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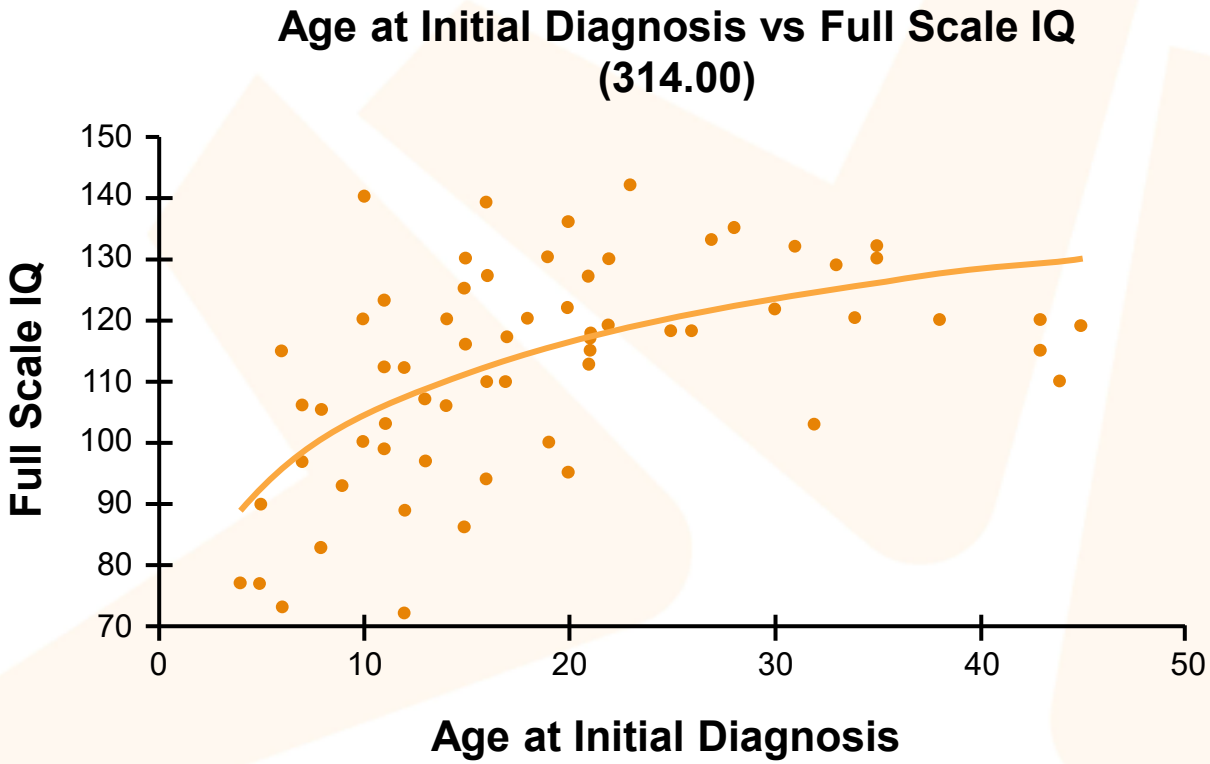
Daily Challenges in Adult ADHD

Adult Onset or Adult Diagnosis of ADHD

Risk factors for adult diagnosis of ADHD:

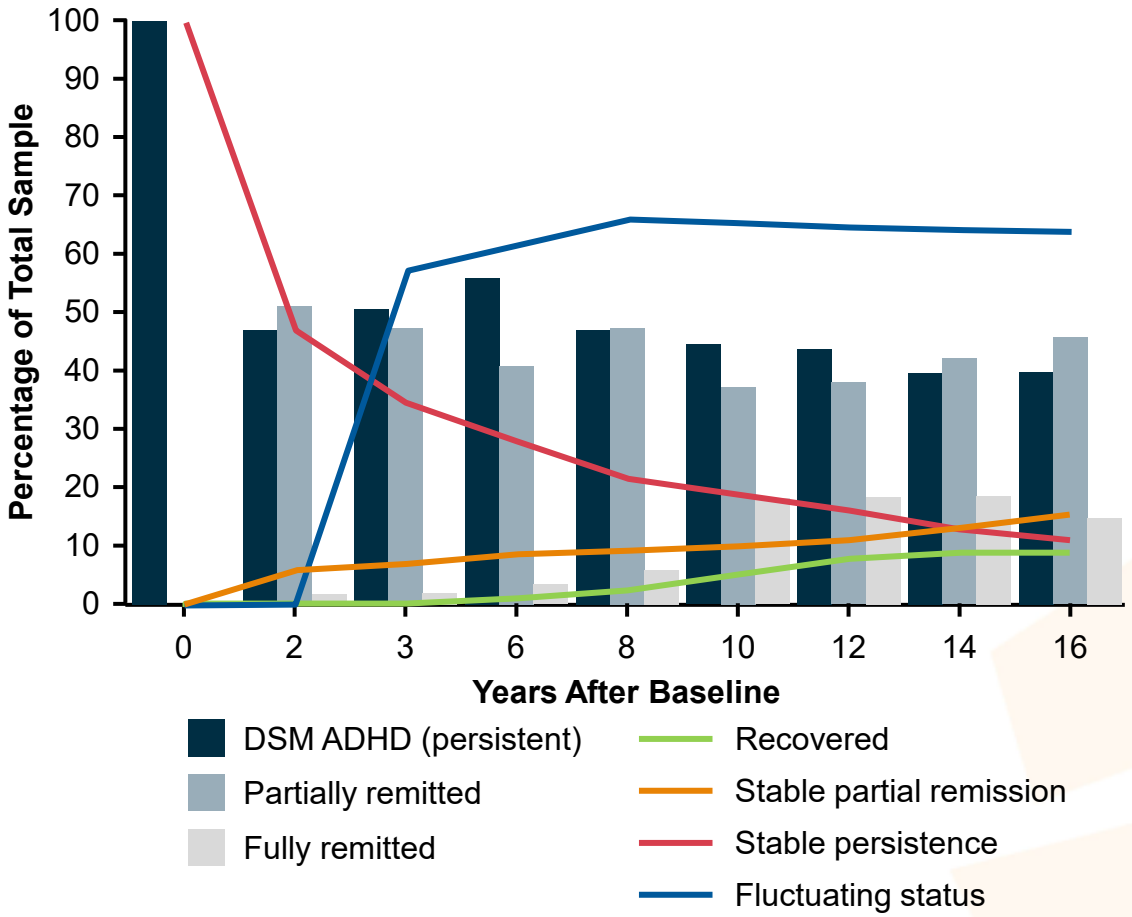
- Female sex
- Higher IQ
- More years of education



KEY TAKE HOME:
IQ can compensate for the impairments of ADHD and forestall diagnosis of ADHD

Breda V, et al. *Br J Psychiatry*. 2021;218(1):43-50. Horrigan JP, et al. Presented at: 47th Annual AACAP Meeting; October 24–29, 2000: New York, New York.

MTA Study Followed into Adulthood



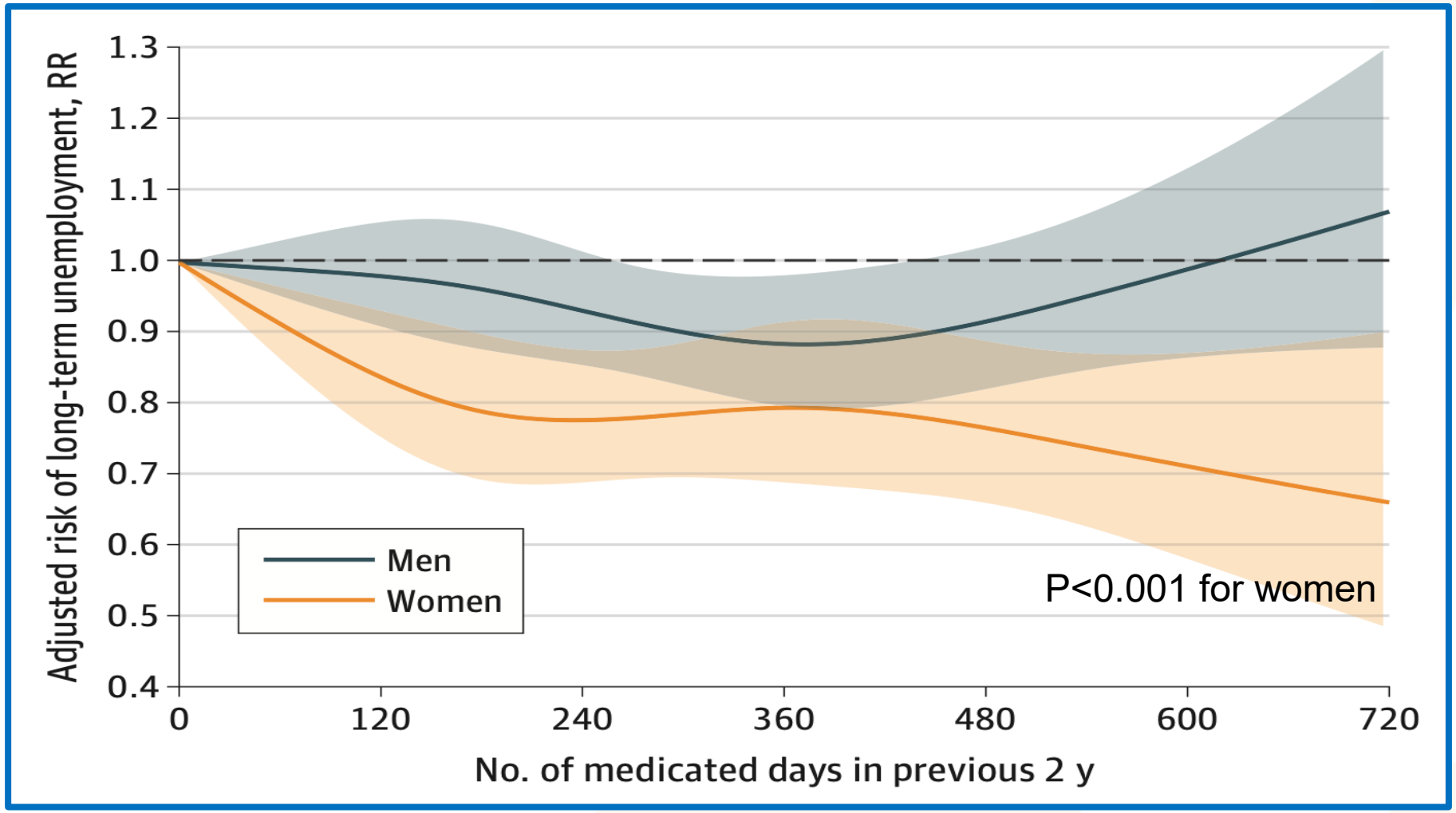
- **9.1%** of demonstrated recovery (sustained remission)
- **10.8%** demonstrated stable ADHD persistence
- **63.8%** had fluctuating periods of remission and recurrence over time

MTA = Multimodal Treatment Study of ADHD.

Sibley MH, et al. *Am J Psychiatry*. 2021 Aug 13; [OAP].

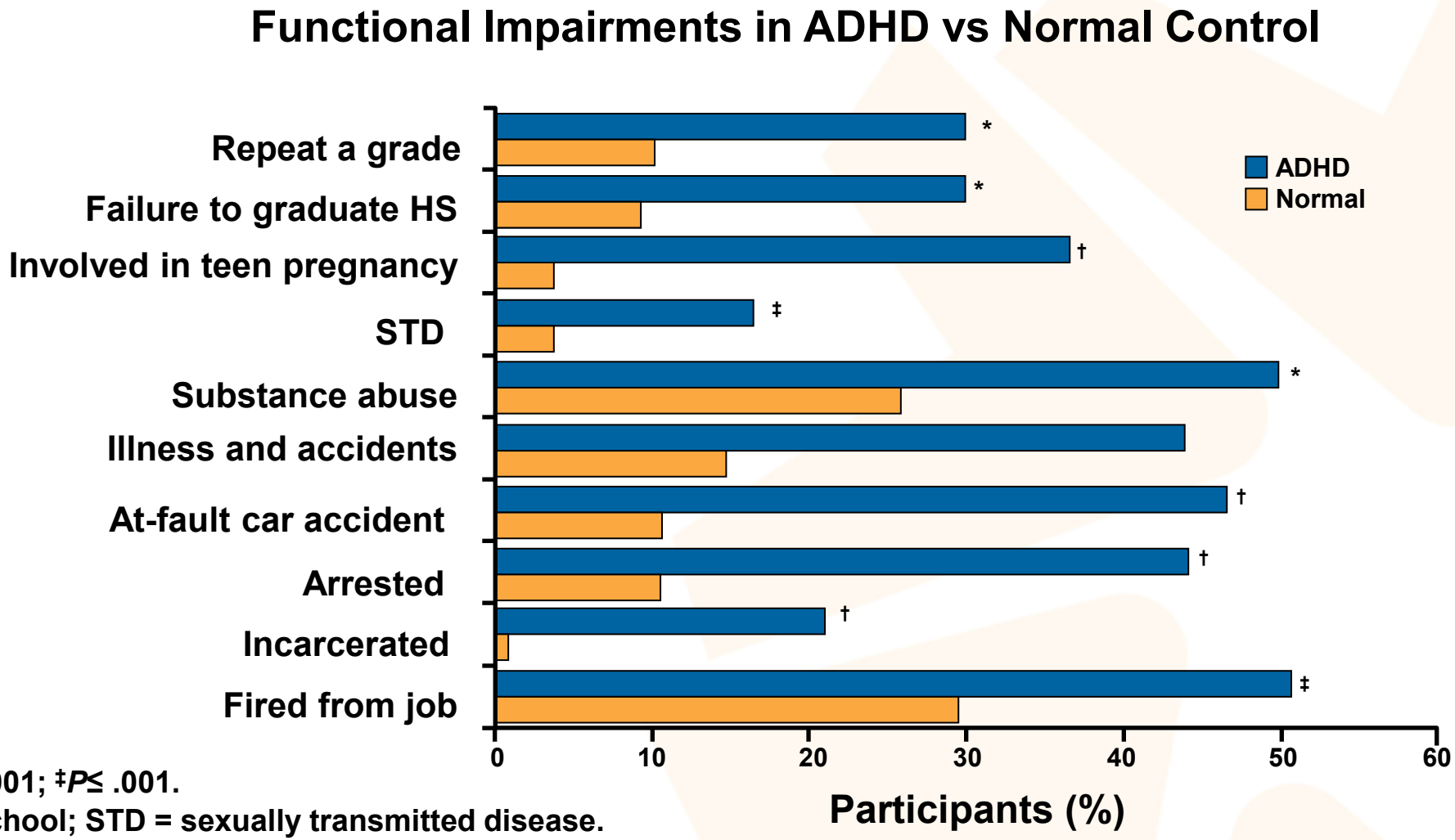
ADHD Affects Men and Women Differently

Unemployment Status



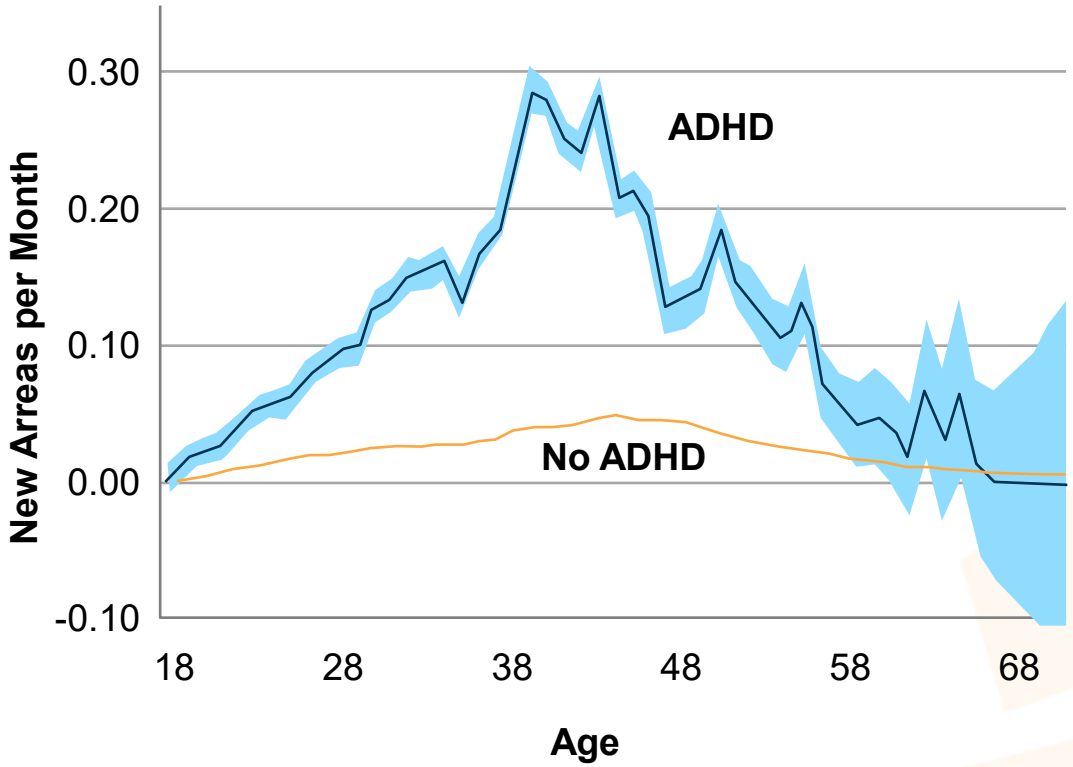
JAMA Network Open. 2022;5(4):e226815.

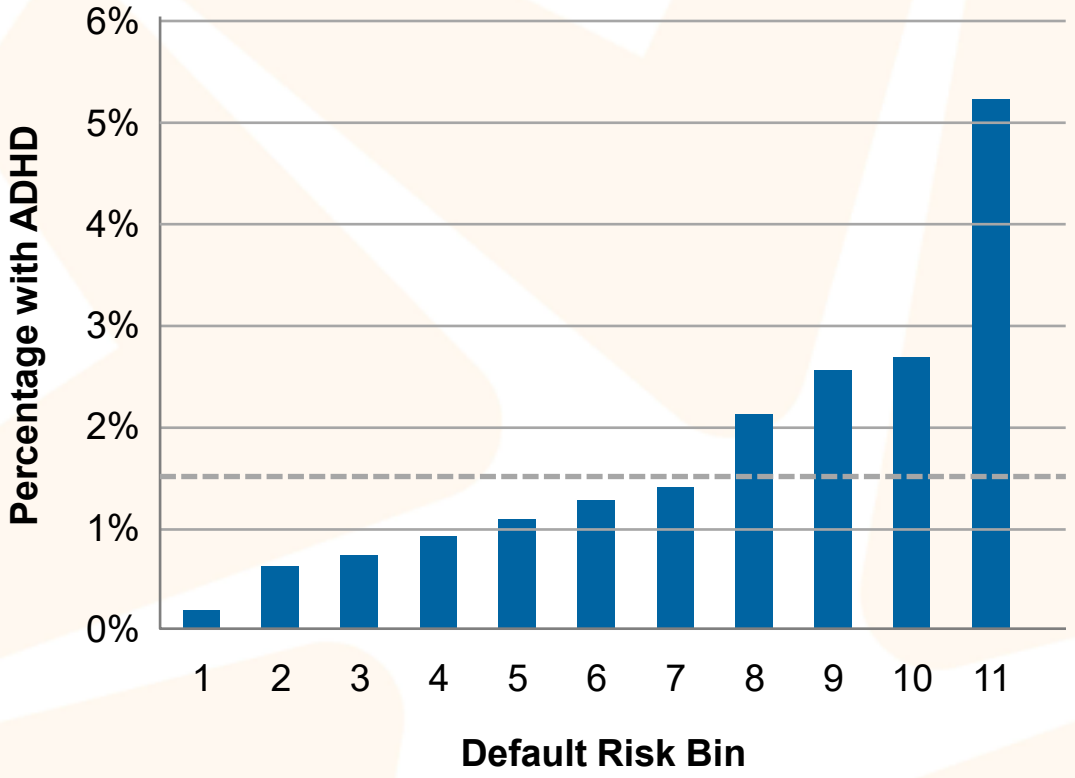
Patients with ADHD Have Greater Rates of Functional Impairment



*$P \leq .01$; †$P \leq .001$; ‡$P \leq .001$.
HS = high school; STD = sexually transmitted disease.
Steele M, et al. *Clin Ther*. 2006;28(11):1892-1908.

Financial Difficulties in Adults with ADHD





Beauchaine TP, et al. *Sci Adv*. 2020;6(40):eaba1551.

Suicide, Homicide, and Unintentional Injury

Outcome or subgroup	Adjusted Model 1	
	HR (95% CI)	P value
All-cause		
Total	1.32 (1.22–1.43)	<0.001
Male	1.26 (1.15–1.39)	<0.001
Female	1.52 (1.28–1.79)	<0.001
Suicide		
Total	2.71 (2.16–3.4)	<0.001
Male	2.48 (1.88–3.28)	<0.001
Female	3.18 (2.13–4.75)	<0.001
Unintentional injury		
Total	1.32 (1.12–1.54)	0.001
Male	1.29 (1.09–1.53)	0.003
Female	1.44 (0.92–2.26)	0.11
Homicide		
Total	2.10 (1.14–3.84)	0.02
Male	1.93 (0.98–3.79)	0.06
Female	3.06 (0.77–12.17)	0.11
Natural causes		
Total	1.14 (1.02–1.27)	0.02
Male	1.09 (0.96–1.24)	0.17
Female	1.28 (1.04–1.58)	0.02

Chen VC, et al. *JAMA Netw Open*. 2019;2(8):e198714.

Psychiatric Comorbidities Increase the Risk of Premature Mortality in Adults with ADHD

Outcome or Subgroup	No. of Deaths	Person-Years	Mortality Rate per 10,000 Person Years	HR (95% CI) Model 1
Overall	3821	16,206,949	2.36	NA
ADHD only	39	102,989	3.79	1.56 (1.11–2.18)
ADHD plus 1 comorbidity	73	57,575	12.68	4.21 (3.27–5.42)
ADHD plus 2 comorbidities	90	29,952	30.05	8.57 (6.73–10.92)
ADHD plus 3 comorbidities	73	14,146	51.60	15.69 (12.08–20.37)
ADHD plus ≥4 comorbidities	94	10,334	90.96	29.29 (22.77–37.66)
None of the above	3452	15,991,953	2.16	1 [Reference]

Sun S, et al. *JAMA Psychiatry*. 2019;76(11):1141-1149.

ADHD Can Look Different in Adults

Common Symptoms in Children

- Self-focused behavior
- Trouble waiting turn
- Emotional turmoil
- Fidgeting
- Problems playing quietly
- Trouble finishing tasks
- Lack of focus
- Forgetfulness

Comorbidities in Children

- Anxiety
- Tics
- Oppositional defiant disorder

Common Symptoms in Adults

- Impulsivity
- Forgetting names and dates
- Missing deadlines and leaving projects unfinished
- Extreme emotionality and rejection sensitivity
- Becoming easily distracted and disorganized
- Low frustration tolerance
- Trouble multitasking
- Excessive activity or restlessness

Comorbidities in Adults

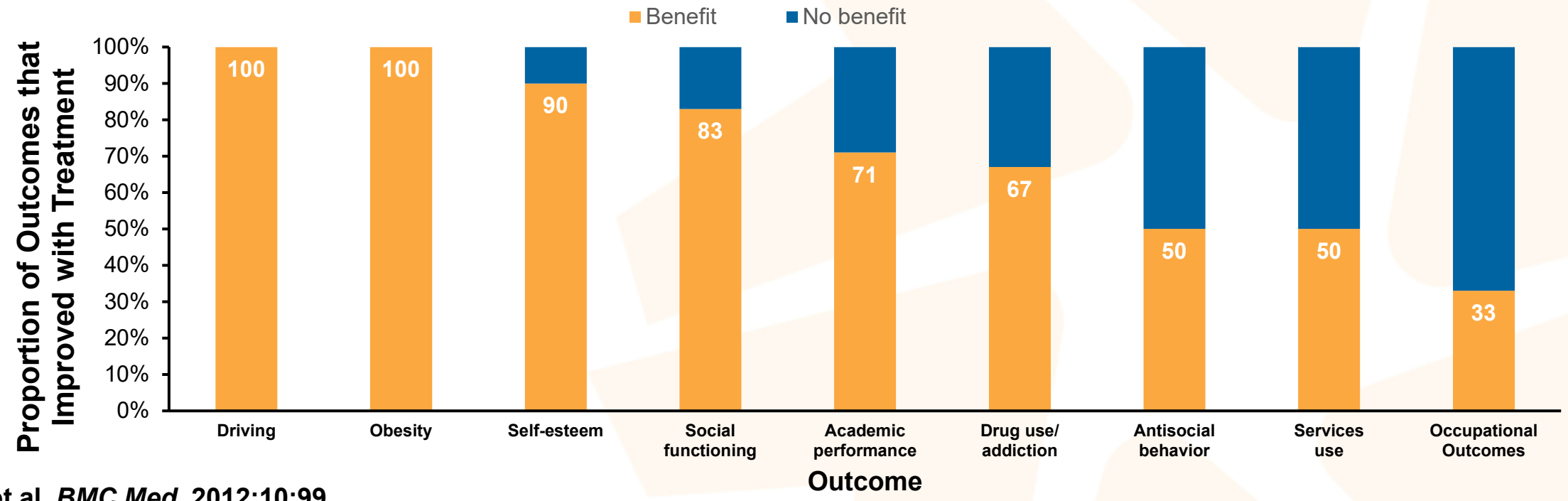
- Depression
- Anxiety
- Bipolar disorder
- Substance use disorders

ADDitude. ADHD in children: symptoms, evaluations & treatments. Updated May 27, 2021. October 2021. Accessed May 27, 2022. www.additudemag.com/adhd-in-children-symptoms-diagnosis-treatment/. ADDitude. ADHD symptoms in adults: ADD checklist & test. August 24, 2021. Accessed May 27, 2022. www.additudemag.com/adult-test-for-add-adhd/. The MTA Cooperative Group. *Arch Gen Psychiatry*. 1999;56(12):1073-1086. Jensen CM, et al. *Atten Defic Hyperact Disord*. 2015;7(1):27-38. Turgay A, et al. *Psychiatry*. 2006;3(4):20-32. Kessler RC, et al. *Am J Psychiatry*. 2006;163(4):716-723.

The Benefits of Treating ADHD

- Treatment of adult ADHD with licensed medications may lead to benefits across a range of outcomes, including core symptoms, executive function, and quality of life, within a relatively short period of time
  - In a systematic analysis of 48 studies and 76 outcome measures in patients with ADHD, treatment of ADHD was associated with benefit in a number of areas

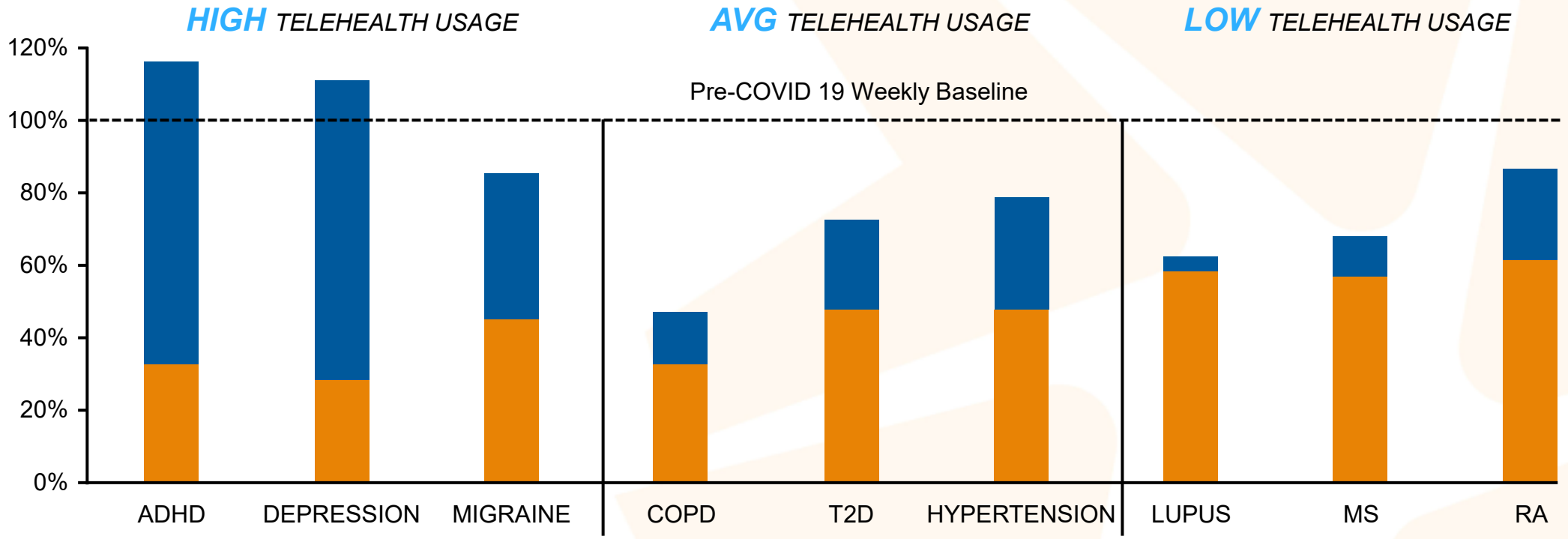
Treatment benefit by outcome group in treated patients with ADHD vs untreated ADHD



Shaw M, et al. *BMC Med*. 2012;10:99.

Telepsychiatry Has Enabled Ongoing Care

Proportion of Claims by Condition Grouping
Office vs Telemedicine
Baseline vs Week Ending 5/1/2020



COPD = chronic obstructive pulmonary disease; MS = multiple sclerosis; RA = rheumatoid arthritis; T2D = type 2 diabetes.
IQVIA Claims Data.

Which is the ‘BEST’ Scale to Detect Inadequate Response to an ADHD Medication?

The one you use consistently!

ADHD-RS ??

ASRS ??

Conner’s ??

BRIEF ??

BADDS ??

CGI ??

Others ??

Johnie

- 27-year-old father
- Presents with a chief complaint of being stressed, anxious, and getting upset
- Struggling at work and home
- Took an SSRI 3 years ago for several months and felt “like it didn’t do much ”
- PHQ-9 = 10 with no SI
- “I get so overwhelmed that I just feel like giving up or I just blow up”
- Asks for something to help with anxiety

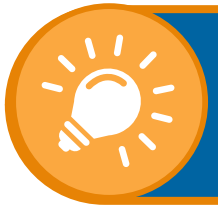
What do you do next?

Further Questions

- Mom with depression and dad was “a drinker”
- 5-year-old son is “a pistol,” and we get a lot of calls from school
- Good athlete but didn’t much like school
- Probably partied a “bit too much”
- Got frustrated and dropped out of college

Barriers to ADHD Recognition

- Screening—You don’t see what you don’t look for!
- Stigma and embarrassment
- “Normalization”—I’ve been this way all my life
- Comorbidity
- Chief complaint—stress, mood, temper, addictions …



KEY TAKE HOME:
Don’t make the rookie mistake and just treat the chief complaint!

What do you do next?

Johnie's Response

Our patient's ADHD-RS score:

- Part A: 15
- Total: 36

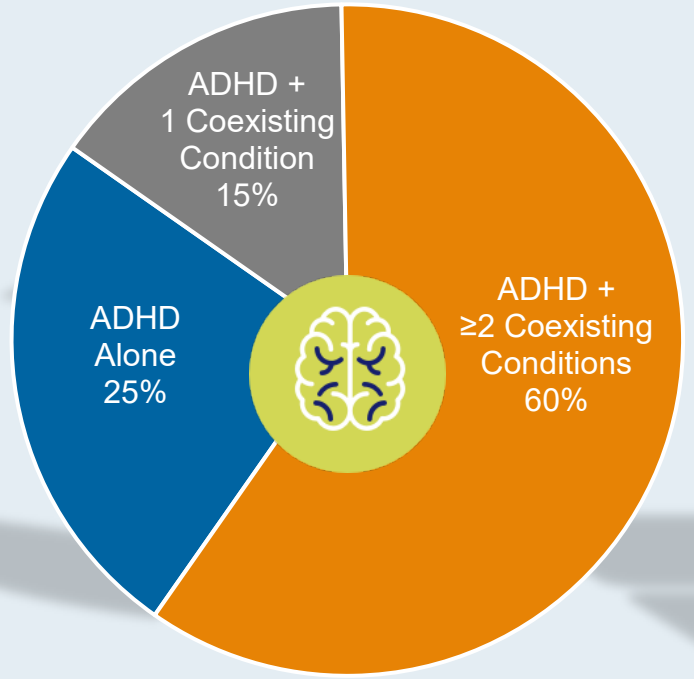
Based on this finding, what would you do next?

1. Refer to psychiatrist
2. Diagnose mild ADHD
3. Diagnose moderate-severe ADHD
4. Initiate trial of short-acting stimulant

	Never	Rarely	Sometimes	Often	Always
1. How often do you have trouble wrapping up the final details of a project, once the challenging parts have been done?				X	
2. How often do you have difficulty getting things in order when you have to do a task that requires organization?				X	
3. How often do you have problems remembering appointments or obligations?			X		
4. When you have a task that requires a lot of thought, how often do you avoid or delay getting started?				X	
5. How often do you fidget or squirm with your hands or feet when you have to sit down for a long time?				X	
6. How often do you feel overly active and compelled to do things, like you were driven by a motor?		X			

ADHD Frequently Occurs with Coexisting Psychiatric Conditions

A Large Proportion of Patients with ADHD Have at Least One Distinctive Comorbid Psychiatric Disorder



MDD
- Enduring dysphoric mood or anhedonia (≥2 weeks)
- Disturbed sleep, appetite
- Suicide-related issues
- Diminished energy levels

GAD
- Exaggerated apprehension, worry (for >6 months)
- Somatic GAD symptoms

ADHD

Bipolar
- Enduring dysphoric or euphoric mood
- Insomnia
- Delusions, grandiosity
- Excessive involvement in pleasurable activities
- Episodic changes from baseline

SUD
- Pathological pattern of substance use with social consequences
- Physiologic, psychologic tolerance, and withdrawal

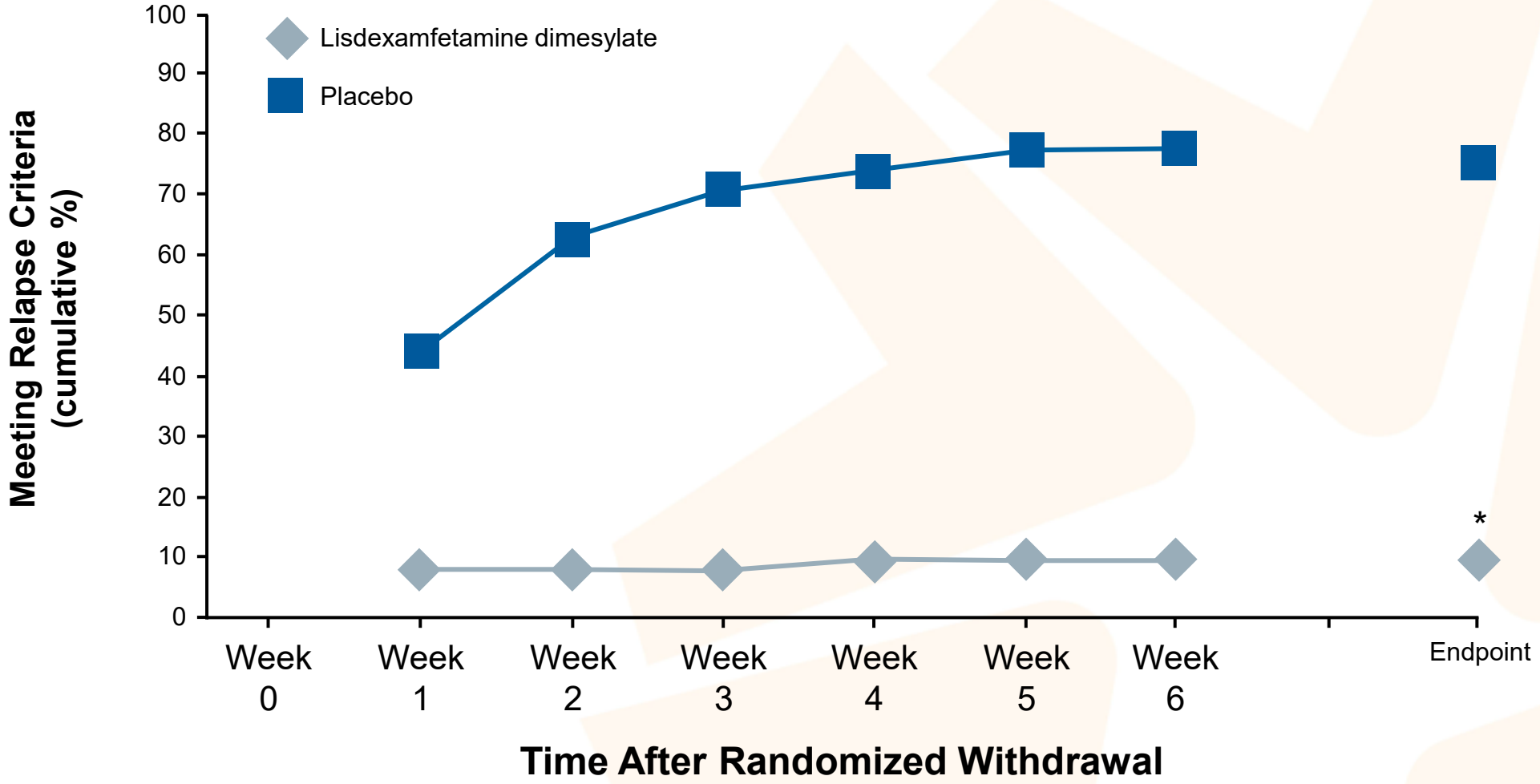
Banaschewski T, et al. *Dtsch Arztebl Int*. 2017;114(9):149-159. Katzman MA, et al. *BMC Psychiatry*. 2017;17(1):302.

5 Common Myths of ADHD

1. Only in boys
   - Twice as common in boys but equally prevalent in adults
   - And girls are more likely to be missed
2. You eventually grow out of it
   - Recent data shows that only 10% of children diagnosed with ADHD do not have ADHD issues as adults
3. Hyperactivity is the outward marker
   - Two thirds of boys have hyperactivity, but the majority of girls do not
4. Try a test dose of a stimulant to see if you focus better
   - Most individuals feel that they focus better with a stimulant, but over time they quickly build a tolerance and need higher and higher doses
5. Only treat when needed
   - Breakthrough symptoms cause impairment

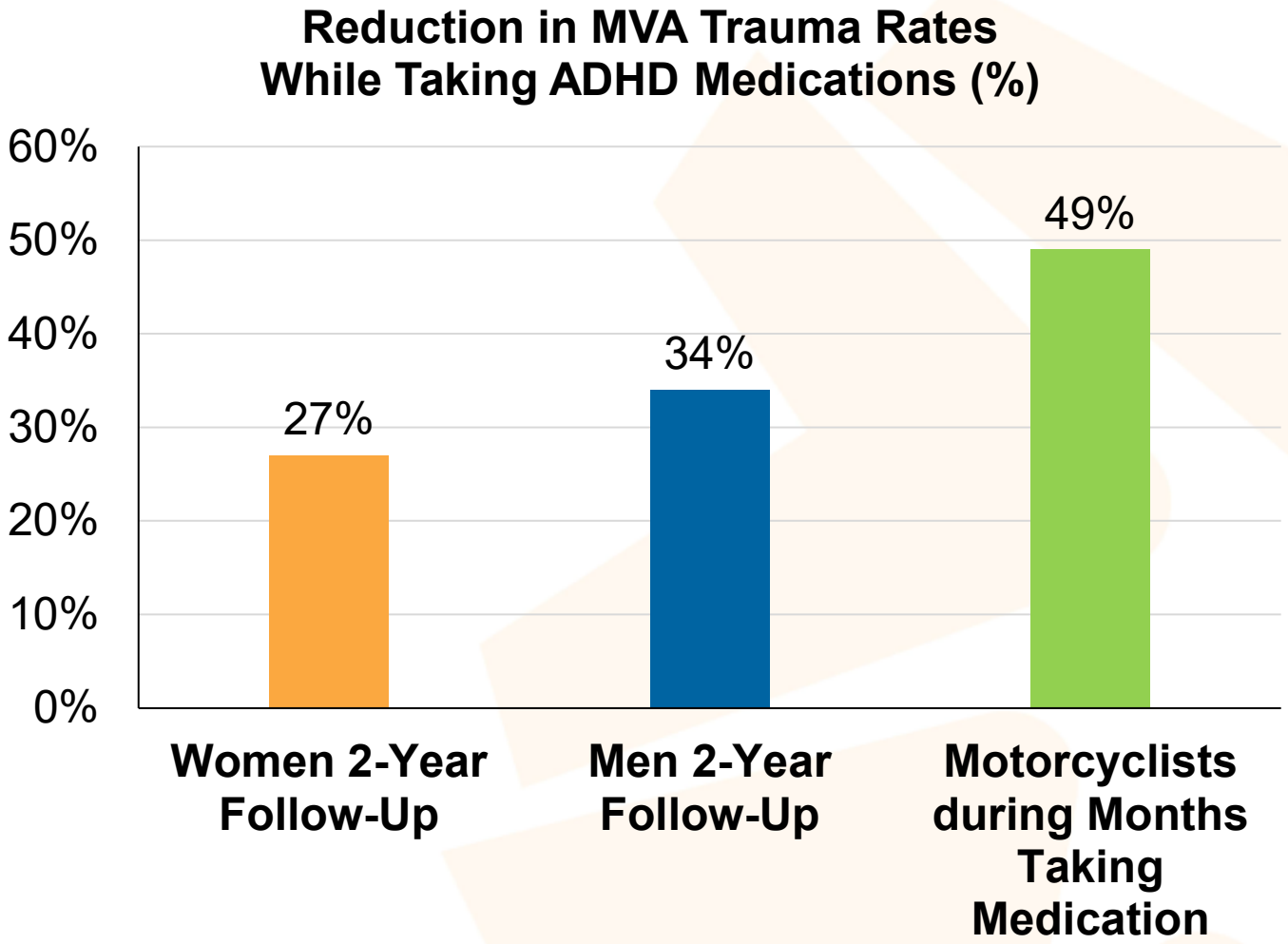
What Happens if You Stop Your Medication?

After >6 Months of Consistent Treatment



Brams M, et al. *J Clin Psychiatry*. 2012;73(7):977-83.

Motor Vehicle Trauma and ADHD Medication Usage



MVA = motor vehicle accidents.

Chang Z, et al. *JAMA Psychiatry*. 2017;74(6):597-603.

ADHD and Anxiety

Considerations and Challenges

- Anxiety exacerbates ADHD-related impairment

Comorbid with ADHD in **~15%** of children and **~47%** of adults

Prescribing Recommendations

- Stimulants can be effective, especially when ADHD symptoms contribute to anxiety
- Long-acting, smooth-release formulations are preferred vs those with distinct phases of drug release
- Titrate slowly, and monitor anxiety as well as ADHD symptoms

"Treatment allows me to hold a thought in my mind long enough to deal with it as thought vs it just slipping into an emotion."

–A mom with ADHD and anxiety

Mattingly GW, et al. *CNS Spectr*. 2021;26(3):202-221.

ADHD and Depression

Considerations and Challenges

- Incidence increases with age

MDD occurs in **19%** of adults with ADHD

Prescribing Recommendations

- **Severe or suicidal cases**: Treating depression takes precedence over ADHD treatment
- **Mild-to-moderate cases**: Treat ADHD and depression concurrently
- Taking both a stimulant and a serotonin reuptake inhibitor is well tolerated, and may address both ADHD and depressive symptoms

A Nationwide Study found that MDD/ADHD patients were twice as likely to be antidepressant nonresponders and nonresponse was cut in half when their ADHD was treated along with their MDD

MDD = major depressive disorder.

Mattingly GW, et al. *CNS Spectr*. 2021;26(3):202-221.

ADHD Treatment Reduces the Risk of Suicidality In Patients with Comorbid ADHD and BD/SZD

Of 1564 BD/SZD patients,

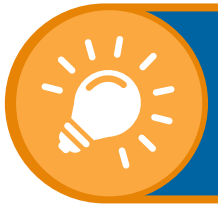
19% of patients (206)

met the criteria for

ADHD & comorbid BD/SZD

Within 6 months after treatment initiation, SA and NSSI events decreased significantly in terms of:

- Number of patients having SA/NSSI (*P*=.013)
- Numbers of SA/NSSI events experienced (*P*=.004)
- Hospitalizations decreased from 31 to 19 (*P*=.029)
- OR=0.63 with stimulant treatment

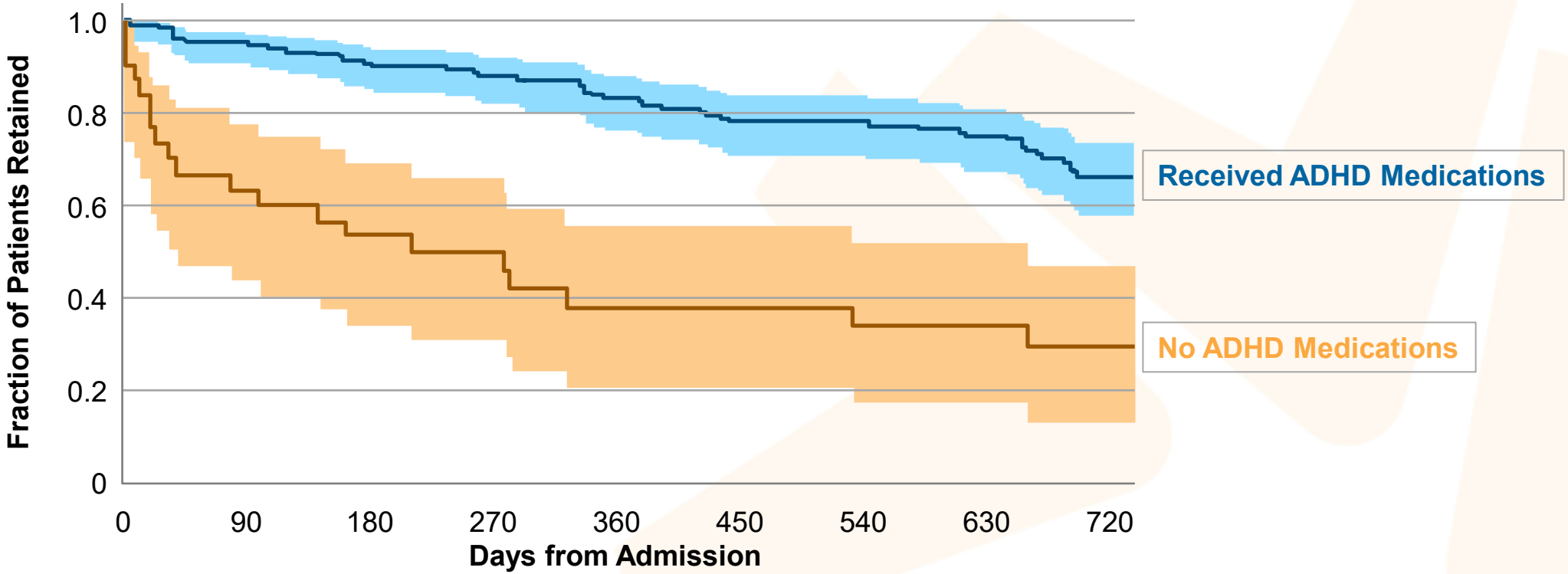


KEY TAKE HOME:
Appropriate ADHD treatment may decrease SA/NSSI in Bipolar/SZD patients who have ADHD

BD = bipolar disorder; NSSI = nonsuicidal self-injury; SA = suicide attempts; SZD = schizoaffective disorder.

Öhlund L, et al. *Ther Adv Psychopharmacol*. 2020 Aug 6;10:2045125320947502.

ADHD and Substance Use

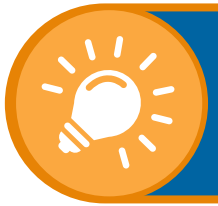


KEY TAKE HOME:
ADHD treatment with a long-acting stimulant tripled the amount of time individuals remained in SUD treatment

Kast KA, et al. *J Clin Psychiatry*. 2021;82(2):20m13598.

ADHD Medications for Adults

1. Consider duration of effect and breakthrough symptoms
2. Peaks and valleys can promote mid-day breakthrough
3. Smoothness on and off can decrease crash and rebound
4. Comorbidity is the rule
5. Adherence is the key



KEY TAKE HOME: **No Short-Acting Stimulant is Approved for Adult ADHD**

Ohlund L, et al. *Ther Adv Psychopharmacol*. 2020;10:2045125320947502.

ADHD Treatment Guide by Age Group

	Considerations & Challenges	Recommended Treatment	Prescribing Considerations
College	• Transition to independent living • At risk for general psychological distress, depression, substance use • Higher risk of ADHD medications misuse/abuse • Poor treatment adherence	• **First-line:** pharmacotherapy with long-acting AMP as first-choice • **If misuse/abuse is a concern:** nonstimulant • **Other options:** Long-acting MPH	• Preplan time and location to receive medication in college • Openly discuss the social and academic benefits of taking medication • Emphasize importance of daily structure, exercise, sleep, and positive peer relations
Adults	• ADHD often undiagnosed and undertreated • High rate of comorbid disorders • Inability to effectively modulate emotions • Excessive mind wandering	• **First-line:** pharmacotherapy with AMP as first-choice • **Other options:** MPH, ATX • **If misuse/abuse is a concern:** ATX	• Determine if ADHD can be treated simultaneously with other comorbid disorder(s) • Consider potential drug–drug interactions of medications for ADHD and comorbid disorders

Mattingly GW, et al. *CNS Spectr*. 2021;26(3):202-221.

Life Transitions and ADHD Management

1. **High School to College**
2. **Living at home to independent living**
3. **Jobs and careers**
4. **Relationships, marriage, and parenting**
5. **Senior living and ADHD**
   - Retirement
   - Structure
   - Purpose
   - Medical comorbidity
   - Memory and aging

Mattingly GW, et al. *CNS Spectr*. 2021;26(3):202-221.

Video Vignette #1

Living with Undiagnosed Adult ADHD

Advances in Treatment of ADHD in Adults

Treatment Guidelines for Adults with ADHD

- [a] A typical sequence of interventions:
  - Education
  - Medication Trial Efficacy/Safety
- [b]Drug treatment is first-line treatment for adults with ADHD with either moderate or severe levels of impairment
- [c]Drug prescribing in adults is supported by British Association Psychopharmacology guidelines

[a]Canadian Attention Deficit Hyperactivity Disorder Resource Alliance (CADDRA). Canadian ADHD Practice Guidelines, Third Edition. Toronto, ON: CADDRA; 2011. www.caddra.ca/pdfs/caddraGuidelines2011.pdf. Accessed March 14, 2019; [b]National Institute for Health and Care Excellence (NICE). Attention deficit hyperactivity disorder: diagnosis and management. March 2018. www.nice.org.uk/guidance/ng87. Accessed March 14, 2019; [c]Bolea-Alamañac B, et al. *J Psychopharmacol*. 2014;28(3):179-203.

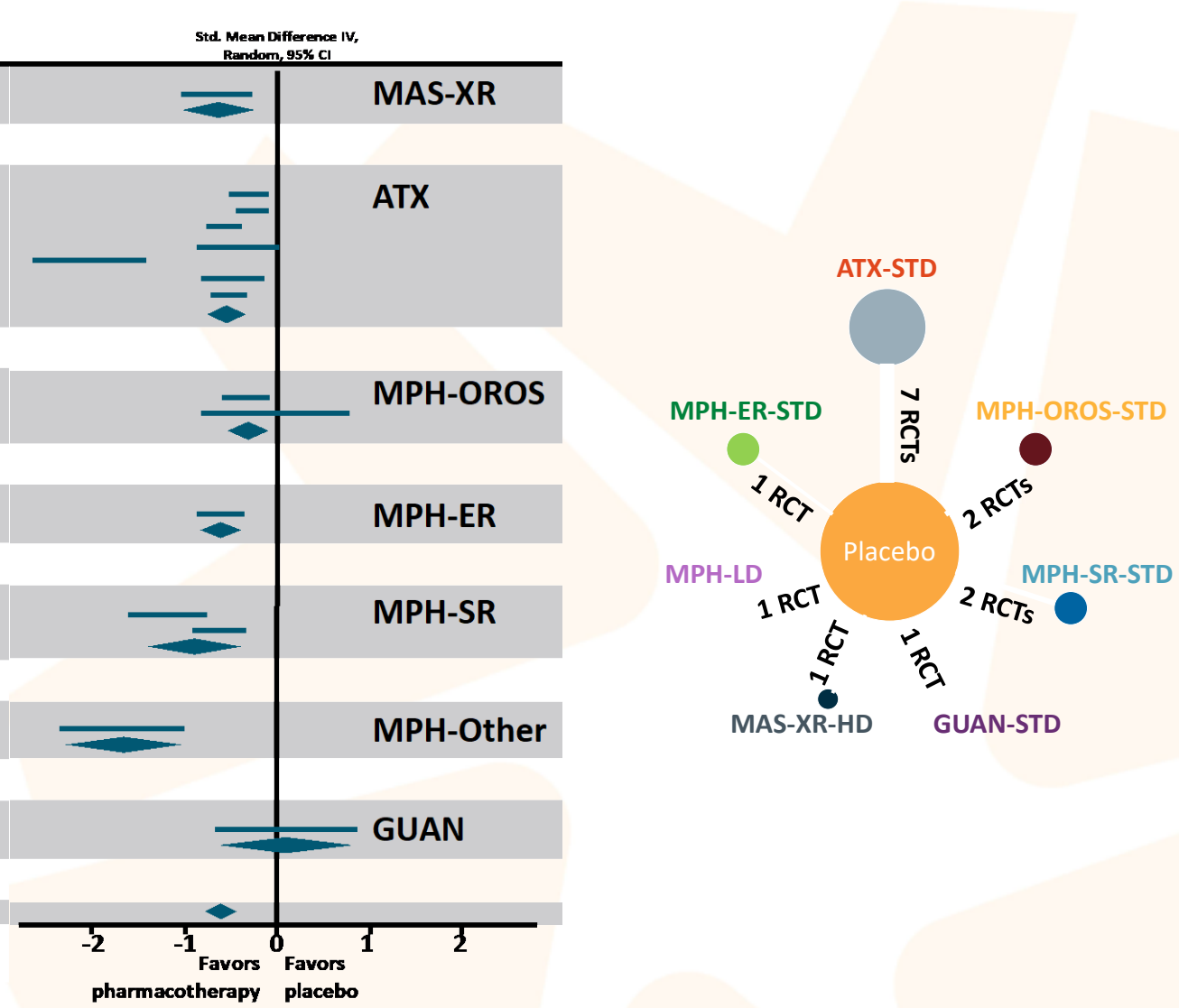
European Adult ADHD Treatment Guidelines: Special Populations

- In patients with ADHD and substance use disorder, to be effective, treatment with stimulants may use higher dosages than normal.
- In patients with ADHD and bipolar disorder, the combined approach of a mood stabilizer with a stimulant has been shown to treat both disorders effectively without inducing (hypo)manic states.
- During pregnancy stimulants are not advised, though large cohort data showed no increased risk for congenital malformations using stimulants during the first trimester. The risk for cardiac malformations using MPH however was slightly increased, while this was not the case for amphetamines.
- Based on data from large cohort studies, following treatment, the negative outcomes associated with ADHD significantly diminish, i.e. traffic accidents, mortality, criminality, depression and suicide, and substance abuse.

Kooij et al. European Psychiatry. 2019;56:14–34.

Meta-analysis of ADHD Treatments in Adults

Study or Subgroup	Pharmacotherapy Mean	SD	Total	Placebo Mean	SD	Total	Weight, %	Std. Mean Difference IV, Random (95% CI)
6.8.1 MAS-XR								
Levin 2015	-16.1	15.3	83	-6	15.8	43	6.6	-0.65 (-1.03 to -0.27)
Subtotal (95% CI)			83			43	6.6	-0.65 (-1.03 to -0.27)
Heterogeneity: Not applicable								
Test for overall effect: Z = 3.37 (*P* = .0007)								
6.8.2 ATX								
Adler 2009, *p.* 212	-8.7	10	224	-5.6	10.2	218	8.8	-0.31 (-0.49 to -0.12)
Adler 2009, *p.* 44	-14.1	13.3	250	-10.5	12.7	251	8.9	-0.28 (-0.45 to -0.10)
Durell 2013	-13.6	7.4	220	-9.3	7.8	225	8.8	-0.56 (-0.75 to -0.37)
McRae-Clark 2010	-15.1	11	39	-11.1	7.6	39	5.8	-0.42 (-0.87 to 0.03)
Sobanski 2012	-13.1	7.7	27	-0.4	4.8	37	4.2	-2.03 (-2.64 to -1.41)
Wilens 2008	-13.6	11.4	72	-8.3	11.4	75	7.2	-0.46 (-0.79 to -0.13)
Young 2011	-14.3	11.8	268	-8.3	11	234	8.9	-0.52 (-0.70 to -0.35)
Subtotal (95% CI)			1100			1079	52.7	-0.55 (-0.77 to -0.33)
Heterogeneity: $Tau^2 = 0.07$; $Chi^2 = 33.42$, df = 6 (*P* <.00001); $I^2 = 82\%$								
Test for overall effect: Z = 4.88 (*P* < 0.00001)								
6.8.3 MPH-OROS								
Casas 2013	-14.1	10.7	182	-10.4	11	97	8.1	-0.34 (-0.59 to -0.09)
Konstenius 2010	-3.9	11.9	12	-4	13.8	12	3.0	0.01 (-0.79, 0.81)
Subtotal (95% CI)			194			109	11.2	-0.31 (-0.55 to -0.07)
Heterogeneity: $Tau^2 = 0$; $Chi^2 = 0.67$, df = 1 (*P* <.41); $I^2 = 0\%$								
Test for overall effect: Z = 2.57 (*P* = .01)								
6.8.4 MPH-ER								
Roster 2009	-18.8	7.2	241	-14.5	6.8	118	8.4	-0.61 (-0.83 to -0.38)
Subtotal (95% CI)			241				8.4	-0.61 (-0.83 to -0.38)
Heterogeneity: Not applicable								
Test for overall effect: Z = 5.29 (*P* <.00001)								
6.8.5 MPH-SR								
Levin 2007	-9.3	2.5	53	-6.2	2.7	53	6.2	-1.18 (-1.60 to -0.77)
Philipsen 2015	-7.3	3.5	110	-5.1	3.4	107	7.8	-0.64 (-0.91 to -0.36)
Subtotal (95% CI)			163			160	14.0	-0.89 (-1.42 to -0.35)
Heterogeneity: $Tau^2 = 0.12$; $Chi^2 = 4.69$, df = 1 (*P* = 0.03); $I^2 = 79\%$								
Test for overall effect: Z = 2.57 (*P* = 0.001)								
6.8.6 MPH-other								
Schrantee 2016 *p.* 955	-0.5	0.4	25	0.1	0.3	24	3.9	-1.66 (-2.32 to -1.01)
Subtotal (95% CI)			25			24	3.9	-1.66 (-2.32 to -1.01)
Heterogeneity: Not applicable								
Test for overall effect: Z = 4.97 (*P* < .00001)								
6.8.7 GUAN								
Butterfield 2016	-10.9	10.9	13	-11.8	9.1	13	3.2	0.09 (-0.68 to 0.86)
Subtotal (95% CI)			13			13	3.2	0.09 (-0.68 to 0.86)
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.22 (*P* = .82)								
Total (95% CI)			1819			1546	100	-0.60 (-0.76 to -0.43)
Heterogeneity: $Tau^2 = 0.07$; $Chi^2 = 65.03$, df = 14 (*P* <.00001); $I^2 = 78\%$								
Test for overall effect: Z = 7.02 (*P* <.00001)								
Test for subgroup differences; $Chi^2 = 19.63$, df = 6 (*P* = .003); $I^2 = 69.4\%$								

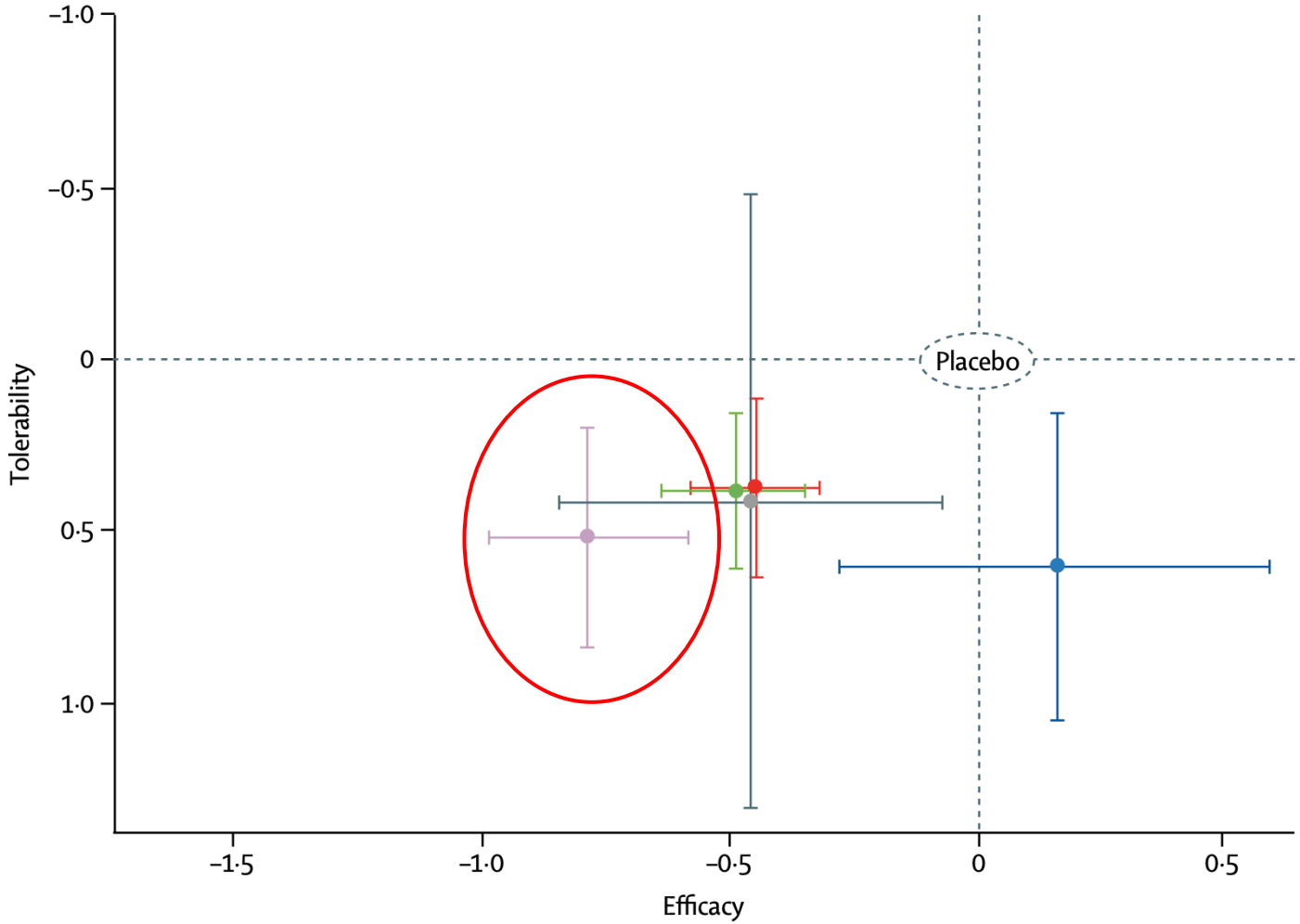


Elliott et al. PLoS ONE. 2020;15:e0240584.

Efficacy and Tolerability of Adult ADHD Treatments

- Amphetamines
- Atomoxetine
- Bupropion
- Clonidine
- Guanfacine
- Methylphenidate
- Modafinil

133 double-blind randomised controlled trials (81 in children and adolescents, 51 in adults, and one in both) were included. The analysis of efficacy closest to 12 weeks was based on 10 068 children and adolescents and 8131 adults; the analysis of tolerability was based on 11 018 children and adolescents and 5362 adults.



Cortese S, et al. *Lancet Psychiatry. 2018;*5:727–38.

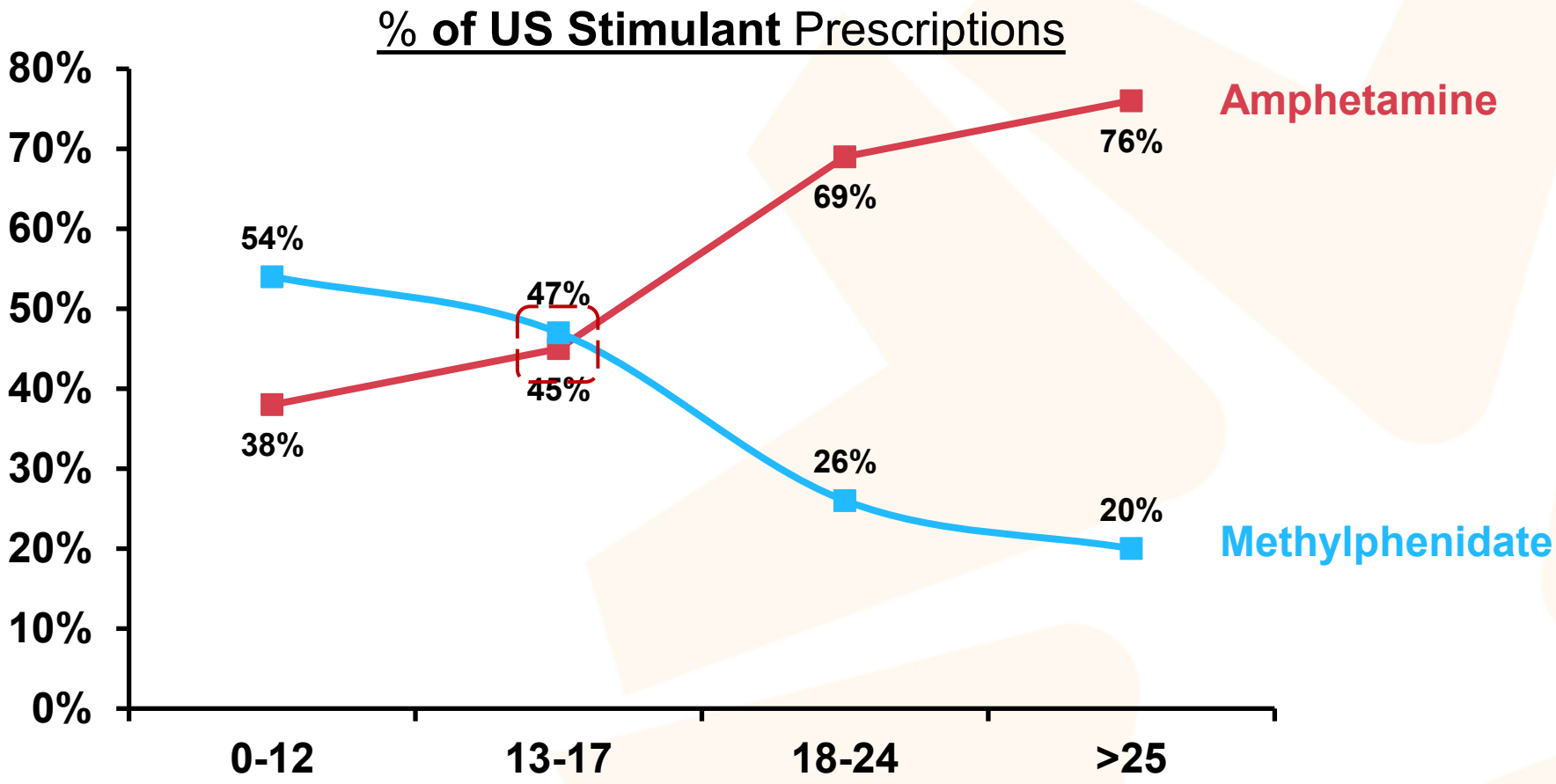
Methylphenidate Preparations

Delivery Mechanism and Formulation	Generic Name	Brand Name	Approved Ages	Dosing (per day)	Onset of Effect	Duration of Effect	Comments	References
Short-acting								
* Dexmethylphenidate tablet	Dexmethylphenidate HCL	Focalin	Children ≥6	2	NA	6 h	At least 4 h between doses	43, 44
* Methylphenidate tablet	Methylphenidate HCL	Ritalin	Children ≥6, adults	2 to 3	1 to 2 h	4 h		45,46
* Methylphenidate chewable tablet and liquid	Methylphenidate HCL	Methylin	Children ≥6, adults	2 to 3	1 h	4 h	Chewable tablet: take with 8 oz of water 30 to 45 min before meals Oral solution: take 30 to 45 min before meals Last dose before 6 PM	47, 48
Intermediate-acting								
* Methylphenidate tablet	Methamphetamine HCL	Methylin ER	Children ≥6, adults	1	NA	NA		49
* Methylphenidate tablet	Methamphetamine HCL	Ritalin-SR	Children ≥6, adults	1	1.5 h	8 h	Take after meals for maximum duration of effect	43, 45
* Methylphenidate tablet	Methamphetamine HCL	Metadate ER	Children ≥6, adults	1	NA	8 h		50
Methylphenidate capsule	Methamphetamine HCL	Metadate CD	Children 6 to 15	1	1.5 h	8 to 9 h	May be sprinkled on applesauce	51, 52
Long-acting								
* Dexmethyl phenidate capsule	Dexmethylphenidate HCL	Focalin XR	Children ≥6, adults	1	30 min	12 h	May be sprinkled	53, 54
* Methylphenidate chewable tablet	Methylphenidate HCL	Quillichew ER	Children ≥6, adults	1	45 min	8 h		55, 56
Methylphenidate chewable tablet	Methylphenidate HCL	Ritalin LA	Children 6 to 12	1	30 min to 1 h	12 h	May be sprinkled	43, 52, 56
* Methylphenidate tablet	Methylphenidate HCL	Concerta	Children ≥6, adults	1	1 to 2 h	10 to 12 h		52, 57
* Methylphenidate liquid	Methylphenidate HCL	Quillivant XR	Children ≥6, adults	1	45 min	12 h	Shake bottle vigorously for 10 s before dispensing	55, 58
Methylphenidate capsule	Methylphenidate HCL	Aptensio XR	Children ≥6, adults	1	1 h	12 h	May be sprinkled	56, 59
* Methylphenidate ODT	Methylphenidate	Cotempla XR-ODT	Children ≥6, adults	1	1 h	12 h	No crushing or chewing Allow to disintegrate in saliva before swallowing	56, 60
Methylphenidate transdermal patch	Methylphenidate	Daytrana	Children ≥6, adults	1	2 h	12 h	Wear for ≤9 h	52, 61
* Methylphenidate capsule	Methylphenidate HCL	Adhansia XR	Children ≥6, adults	1	1 h	13 to 16 h	May be sprinkled and consumed within 10 min	62
* Methylphenidate capsule	Methylphenidate HCL	Jornay PM	Children ≥6, adults	1	8 to 10 h	12+ h	Take in the evening between 6:30 and 9:30 PM for early morning symptom control May be sprinkled	63, 64

***Approved in adults.** **ODT = Oral disintegrating tablet.**

Mattingly GW and Young J. 2021. CNS Spectrums 26(2), 104-114.

Transition from Methylphenidate to Amphetamine Occurs in Adolescence



Data Source: IMS NPA Market Dynamics - RETAIL Rx ONLY. Mattingly GW, et al. *CNS Spectr*. 2016;21(S1):45-59.

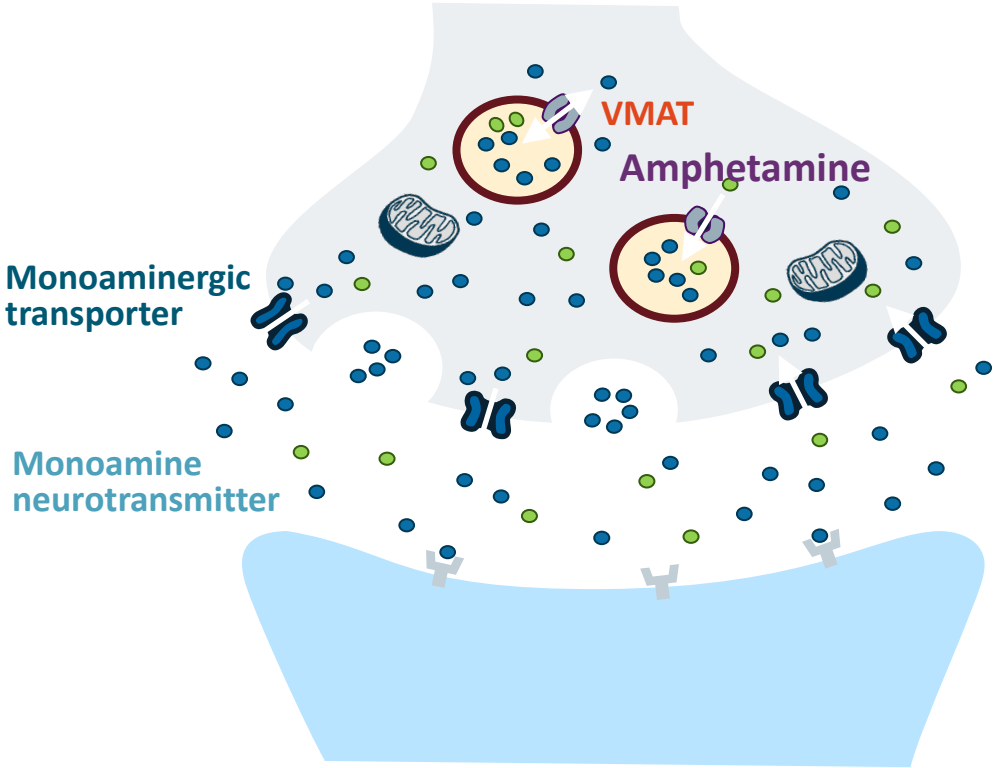
Amphetamine Preparations

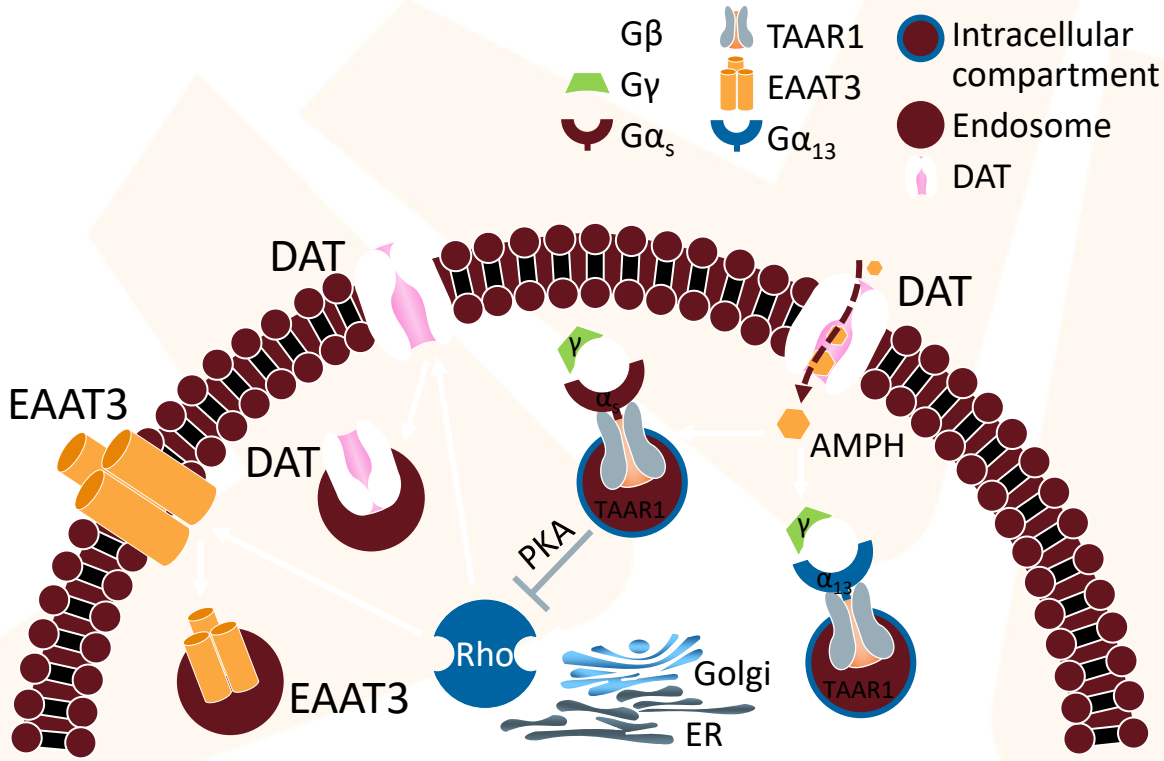
Delivery Mechanism and Formulation	Generic Name	Brand Name	Approved Ages	Dosing (per day)	Onset of Effect	Duration of Effect	Comments	References
Short-acting								
Amphetamine tablet	Amphetamine mixed salts	Adderall	Children ≥3	1 to 3	1.5 h	4 to 6 h	Elimination half-life 9.77 to 11 h for the D-isomer and 11.5 to 13.8 h for the L-isomer	65-68
Dextroamphetamine tablet	Dextroamphetamine sulfate	Dexedrine	Children 3 to 16	1 to 2	NA	4 to 6 h		67, 69
Dextroamphetamine tablet	Dextroamphetamine sulfate	Zenzedi	Children 3 to 16	1 to 3	NA	4 to 6 h		70
Dextroamphetamine liquid	Dextroamphetamine sulfate	ProCentra	Children 6 to 16	1 to 2	NA	6 to 10 h	Plasma half-life of approximately 12 h	71
Methamphetamine tablet	Methamphetamine HCL	Desoxyn	Children ≥6	1 to 2	NA	NA	Not readily available	72
Intermediate-acting								
Amphetamine tablet and ODT	Racemic amphetamine sulfate	Evekeo	Children ≥3 (tablet) Children 6 to 17 (ODT)	1 to 2	45 min	9.25 h	Elimination half-life 10.0 to 11.7 h	73-75
Dextroamphetamine capsule	Dextroamphetamine sulfate	Dexedrine spansule	Children 6 to 16	1 to 2	NA	6 to 10 h	Plasma half-life of approximately 12 h	67, 69
Long-acting								
* Amphetamine capsule	Amphetamine mixed salts	Adderall XR	Children ≥6, adults	1	1.5 h	10.5 to 12 h	May be sprinkled on applesauce	53, 54
* Amphetamine liquid	Amphetamine	Adzenys ER	Children ≥6, adults	1	1.5 h	10 to 12 h	Do not add to food or other liquids	55, 56
* Amphetamine ODT	Amphetamine	Adzenys XR-ODT	Children 6 to 12	1	1.5 h	10 to 12 h	Allow tablet to disintegrate in saliva before swallowing	43, 52, 56
Amphetamine liquid	Amphetamine	Dyanavel XR	Children ≥6, adults	1	1 h	12 h		52, 57
* Amphetamine capsule	Amphetamine mixed salts	Mydayis	Children ≥6, adults	1	2 h	14 h	May be sprinkled on applesauce	55, 58
* Amphetamine prodrug capsule and chewable tablet	Lisdexamfetamine dimesylate	Vyvanse	Children ≥6, adults	1	1.5 to 2 h	12 to 14 h	Capsule: may be sprinkled in water, orange juice, or yogurt Chewable tablet: chew thoroughly before swallowing	56, 59

*Approved in adults. ODT = Oral disintegrating tablet.

Mattingly GW and Young J. 2021. CNS Spectrums 26(2), 104-114.

Updated Mechanism of Action of Amphetamines



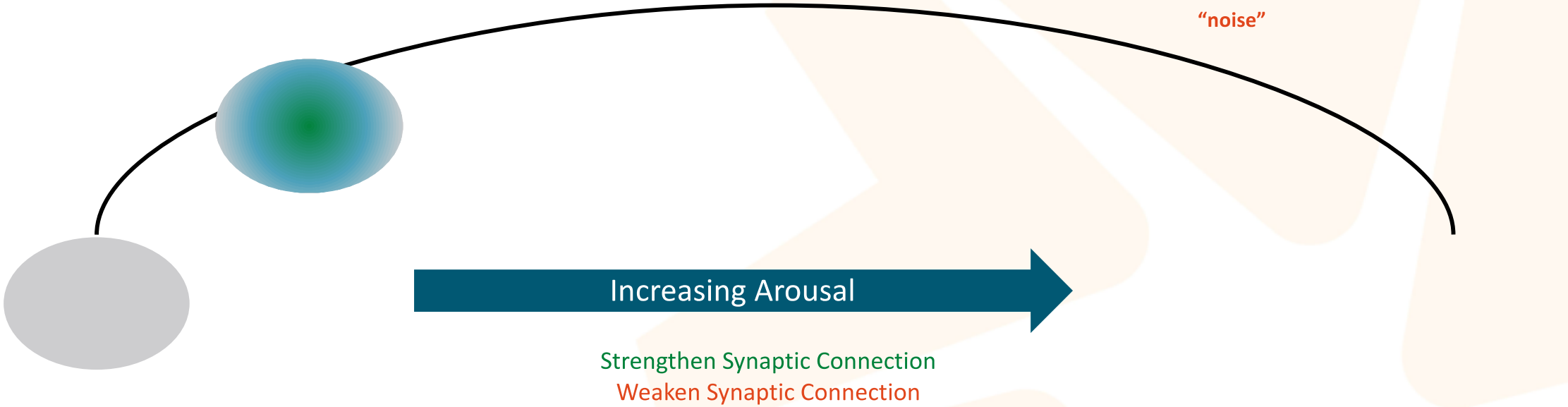


Amphetamines access the neurotransmitter vesicles inside neuron via the VMAT, promoting disruption of vesicular storage increasing the free cytosol neurotransmitter content. The free neurotransmitter content is also increased by the inhibition of MAO metabolism promoted by amphetamines. Given the massive increase of neurotransmitter in the cytosol the monoamine transporter activity is reversed and promotes the non-vesicular release of neurotransmitters.

Teixeira-Gomes. Int J Dev Neurosci. 2015;41:44. Underhill. Mol Psychiatry. 2021;26:1208.

Treating ADHD and Comorbidities: Neurobiological Basis for Informed Polypharmacy

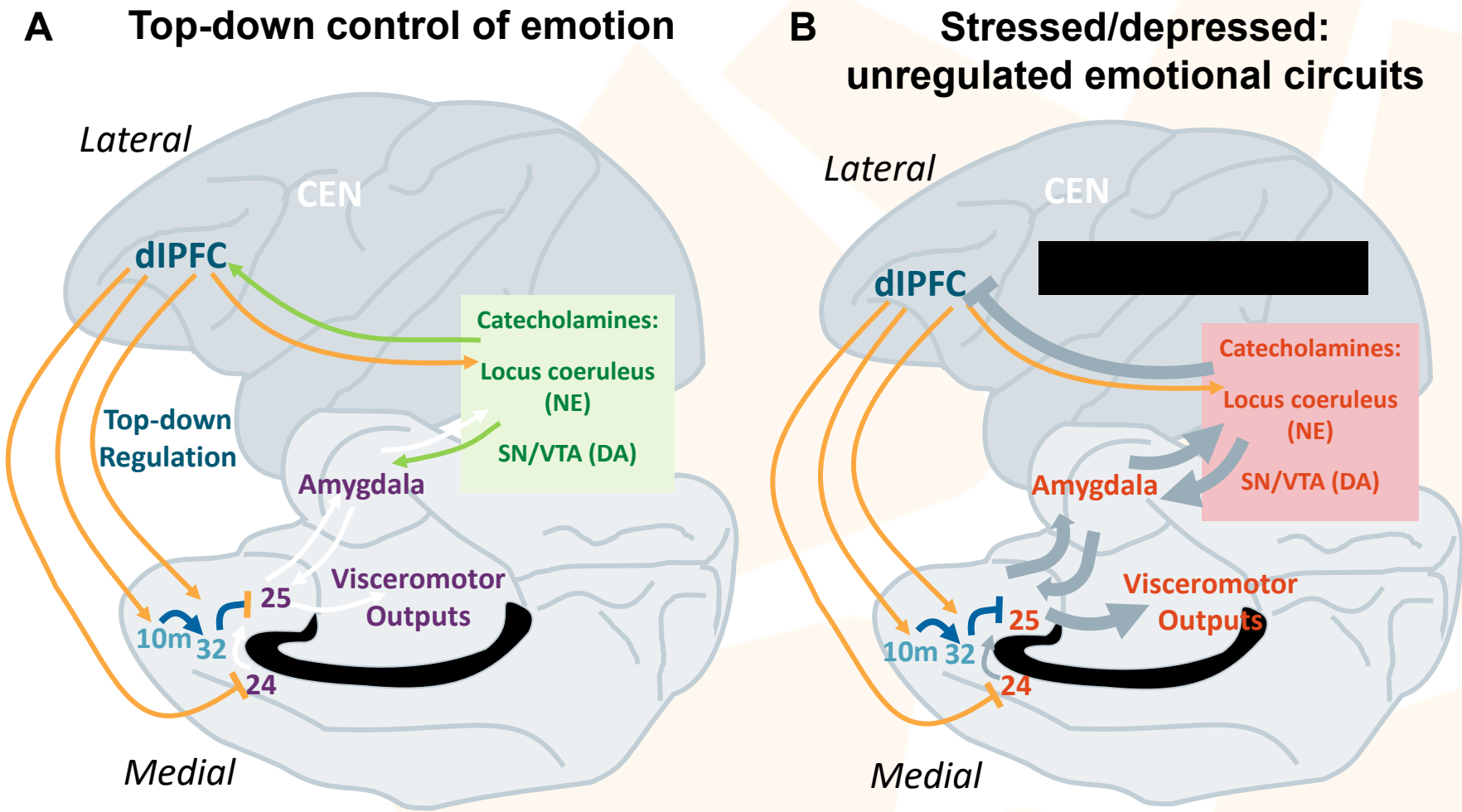
Catecholamine Regulation of PFC Activity and Sensory Circuits: Is there Too Much of a Good Thing?



Cools. *Neuropsychopharmacology.* 2021;47:309. Waterhouse. *Brain Res*. 2019;1709:1.

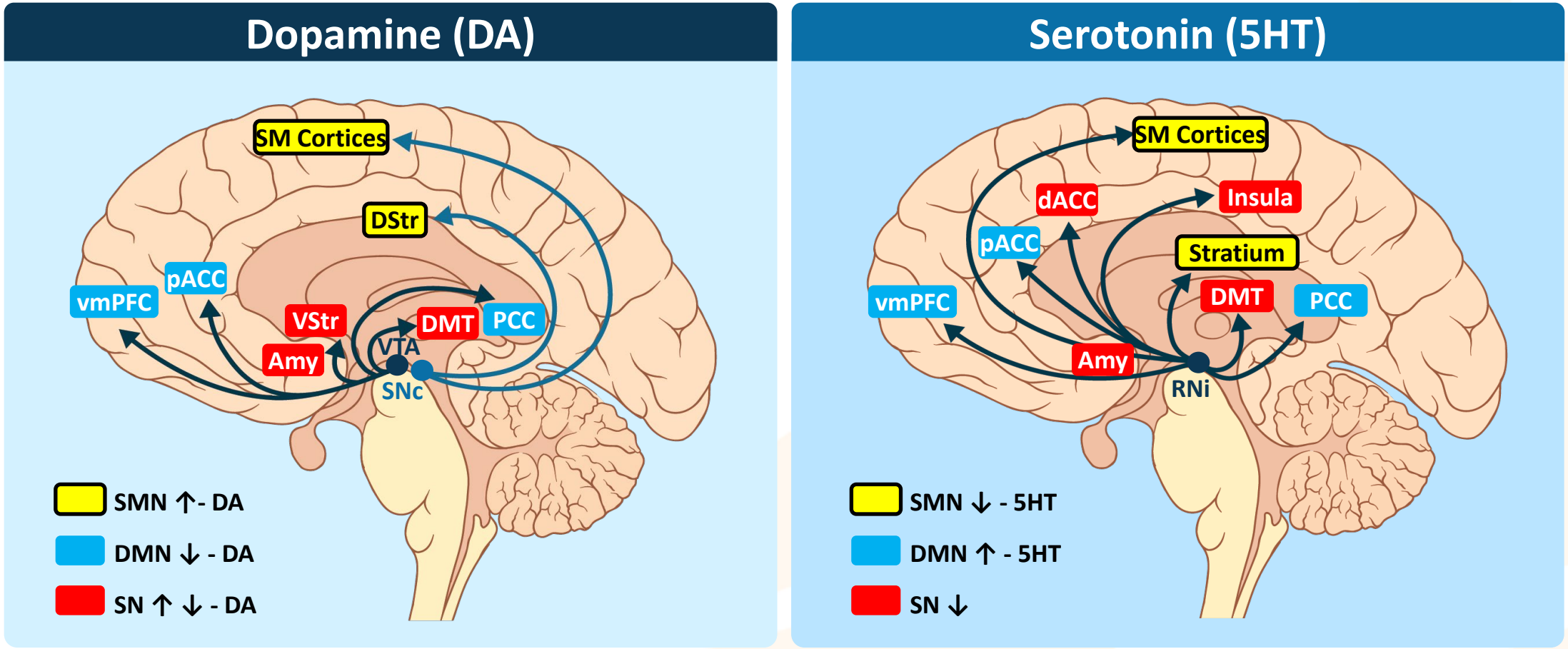
Reflective to Reactive: Catecholamine Regulation of Prefrontal Cortex, Limbic and Paralimbic Areas

Anterior cingulate cortex BA24; BA25 (subgenual cingulate); BA10 frontopolar or dorsomedial PFC: dlPFC dorsolateral PFC; BA32 dorsal anterior cingulate; SNc substantia nigra pars compacta, supplies striatum with dopamine; CEN central executive network



Adapted from: Yang S, et al. Front Psychiatry. 2021;12: 654322.

5-HT and DA Have a Role in Networks Associated With ADHD, Comorbidities and Treatments



dACC = dorsal anterior cingulate cortex; DMN = default mode network; DMT = dorsomedial thalamus; DStr = dorsal striatum; pACC = perigenual anterior cingulate cortex; PCC = posterior cingulate cortex; Rni = raphe nuclei; RSNs = resting state networks; SM = sensorimotor; SMN = sensorimotor network; SN = salience network = SNc, substantia nigra pars compacta; vmPFC = ventromedial prefrontal cortex; VStr = ventral striatum; VTA = ventral tegmental area; Amy = amygdala.

Adapted from: Conio et al. 2020, Mol Psychiatry;25: 82-93.

Managing Common Side Effects

Appetite Loss	Insomnia*	Stomachaches	Tics*

• Patience
  • Usually improves after a few days
• Eat a big breakfast and delay dinner
• Adjust timing of medication
• Adjust timing of meals
• Encourage snacks (including bedtime)
• Consider changing dose, regimen, or medication
	• Melatonin
	• Clonidine, guanfacine
	• Trazodone
	• Mirtazapine
	• Antihistamine (acutely)
	• Tricyclic antidepressant
		• Direct vs indirect effect
		  • Medication vs hunger
		  • Determine time of day
		• Patience
		  • Often resolve after the first few days of treatment
		• Lower daily dose
		• Try a different medication
			• Stimulant-exacerbated tics
			  • Examine severity of tics
			  • Re-challenge to examine if tics are stimulant-induced
			  • Switch to atomoxetine, α2-adrenergic agonists, or atypical or typical antipsychotics (pimozide – FDA approved)
			  • Combination therapies
			  • Atomoxetine plus stimulant
			  • Clonidine plus MPH (3 studies)
			  • Atypical plus other treatment

***The use of these medications for this indication is off-label.**

Pliszka SR. *J Am Acad Child Adolesc Psychiatry.* 2006;46(7):894-921. Daughton J, et al. In: Martin A, et al (Eds). *Pediatric Psychopharmacology: Principles and Practice*. Second Edition. New York, NY: Oxford Press; 2011. Weiss MD, et al. *J Am Acad Child Adolesc Psychiatry*. 2006;45(5):512-519. Tjon Pian Gi CV, et al. *Eur J Pediatr*. 2003;162(7-8):554-555. Kratochvil CJ, et al. *J Am Acad Child Adolesc Psychiatry*. 2005;44(5):499-501. Palumbo DR, et al. *J Am Acad Child Adolesc Psychiatry*. 2008;47(2):180-188. Hazell PL, et al. *J Am Acad Child Adolesc Psychiatry*. 2003;42(8):886-94. The Tourette's Syndrome Study Group. *Neurology*. 2002;58(4):527-536.

Switching Medications

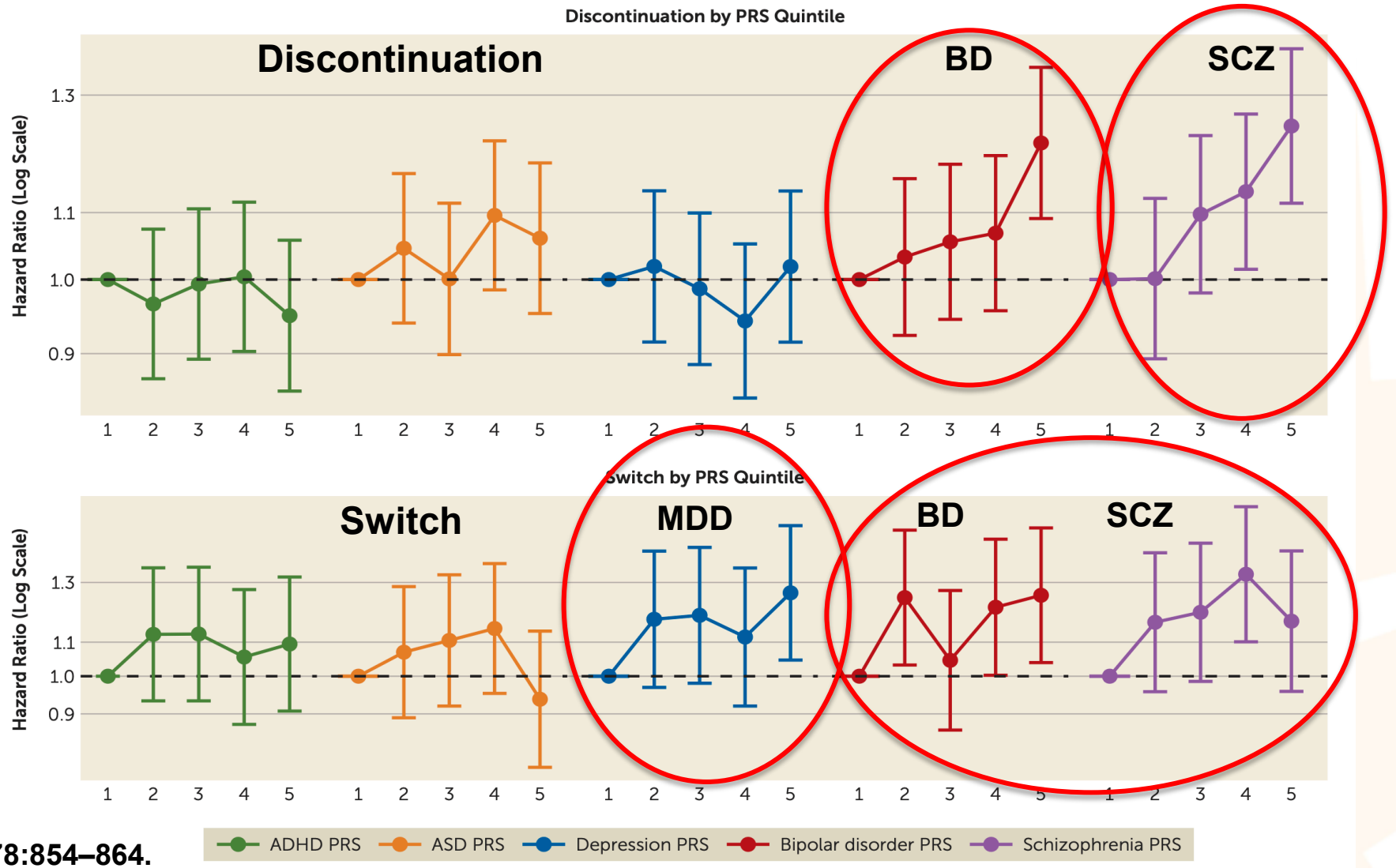
Questions to Ask Before Switching to Non-Stimulants Or Adding Augmenting Strategies

1. Have I titrated properly?
2. Is the patient at the maximum dose?
3. Is this drug/preparation working well at any times during the day and do I need to change the dose or preparation to get a more balanced effect?
4. Am I targeting the right symptoms?
5. Is there a behavioral explanation for the drug “wearing off” or is the patient becoming tolerant to this medication?
6. What else is going on in patient’s life/family life, and are there non-pharmacological reasons for poor response?
7. Have I missed a comorbidity?

Cortese S, et al. CNS Drugs. 2021;35:1035–1051.

Which Patients/Parents/Clinicians Living with or Affected by ADHD Decide to Switch or Stop Medications?

The authors obtained genetic and national register data for 9,133 individuals with ADHD from the Danish iPSYCH2012 sample and defined stimulant treatment initiation, discontinuation, and switch from prescriptions. For each stimulant treatment outcome, they examined associations with polygenic risk scores (PRSs) for psychiatric disorders and clinical and sociodemographic factors.



Brikell I, et al. Am J Psychiatry. 2021;178:854–864.

Stimulant Misuse and Stigma of ADHD

Key Learning Point

Long-acting/extended-release formulations of stimulants minimize abuse/misuse potential

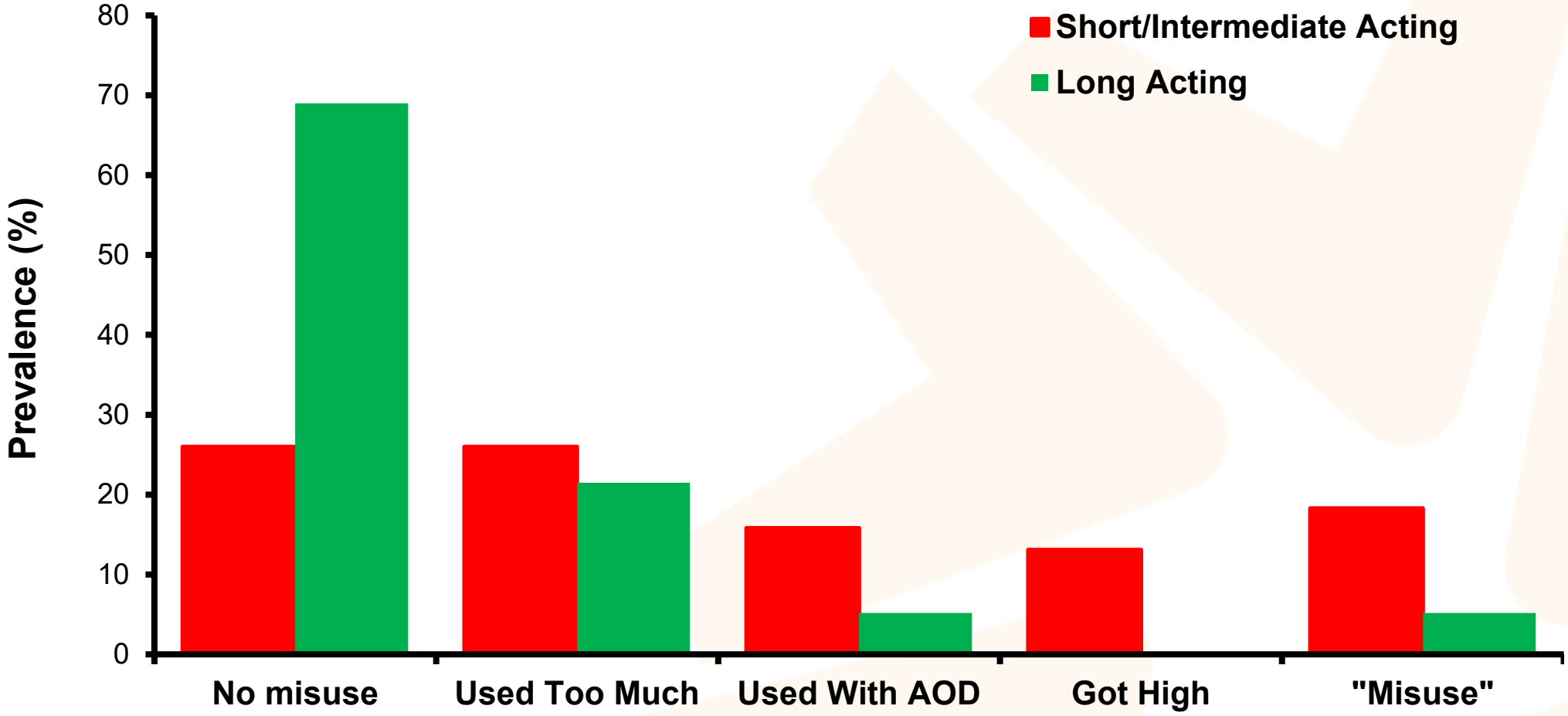
Stimulants Prescribed for ADHD Risk Factors for Misuse and Diversion

- Rates of past year nonprescribed stimulant use:
  - 5% to 9% of grade- and high-school age children
  - 5% to 35% of college-age individuals
- Lifetime rates of diversion:
  - 16% to 29% of students with prescriptions asked to give, sell, or trade medications

- Risk Factors:
  - White race
  - Membership in a fraternity or sorority
  - Lower grade point averages
  - Use of IR compared with ER preparations
  - Individuals with multiple ADHD symptoms

Faraone SV, et al. *J Clin Psychiatry*. 2003;64(Suppl 11):9-13. SAMHSA. *Results from the 2010 National Survey on Drug Use and Health: Summary of National Findings*. NSDUH Series H-41, HHS Publication No. (SMA) 11-4658. Rockville, MD: Substance Abuse and Mental Health Services Administration, 2011. Wilens TE, et al. *Pediatrics*. 2003;111(1):179-185.

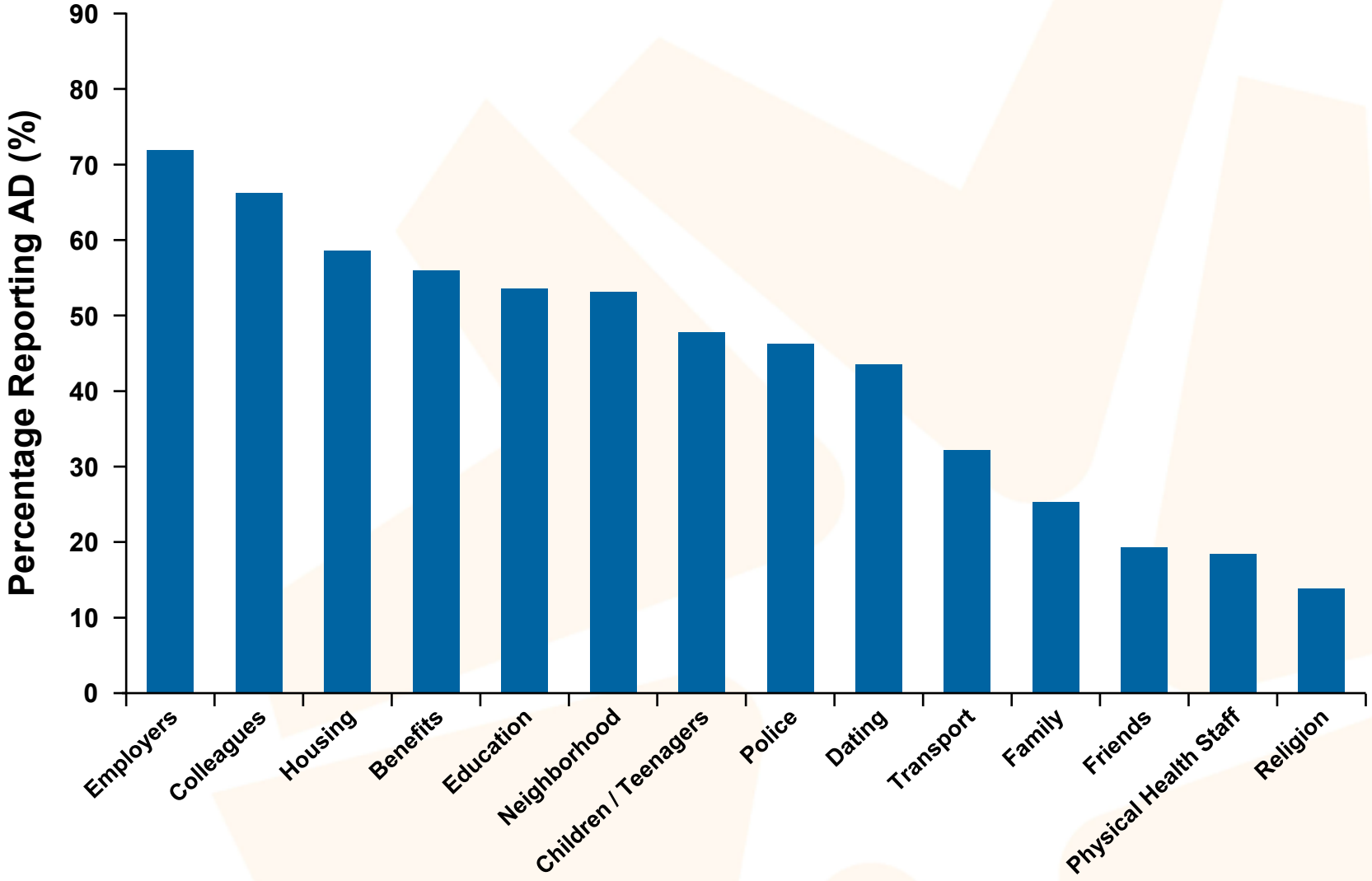
Stimulant Misuse and Abuse in Treated College Students



N = 55 past-year prescribed stimulant users from a random sample at a large Midwestern research university.
AOD = alcohol and other drugs
Sepulveda DR, et al. *J Pharm Pract*. 2011;24(6):551-560.

Internalized Stigma in Adults with ADHD

The sample comprised *n* = 104 adults with ADHD, of whom *n* = 24 (23.3%) reported high internalized stigma, *n* = 92 (88.5%) anticipated discrimination in daily life and *n* = 70 (69.3%) perceived public stigma. Percentage of participants reporting anticipated discrimination (AD) per life domain in the Questionnaire on Anticipated Discrimination (QUAD)



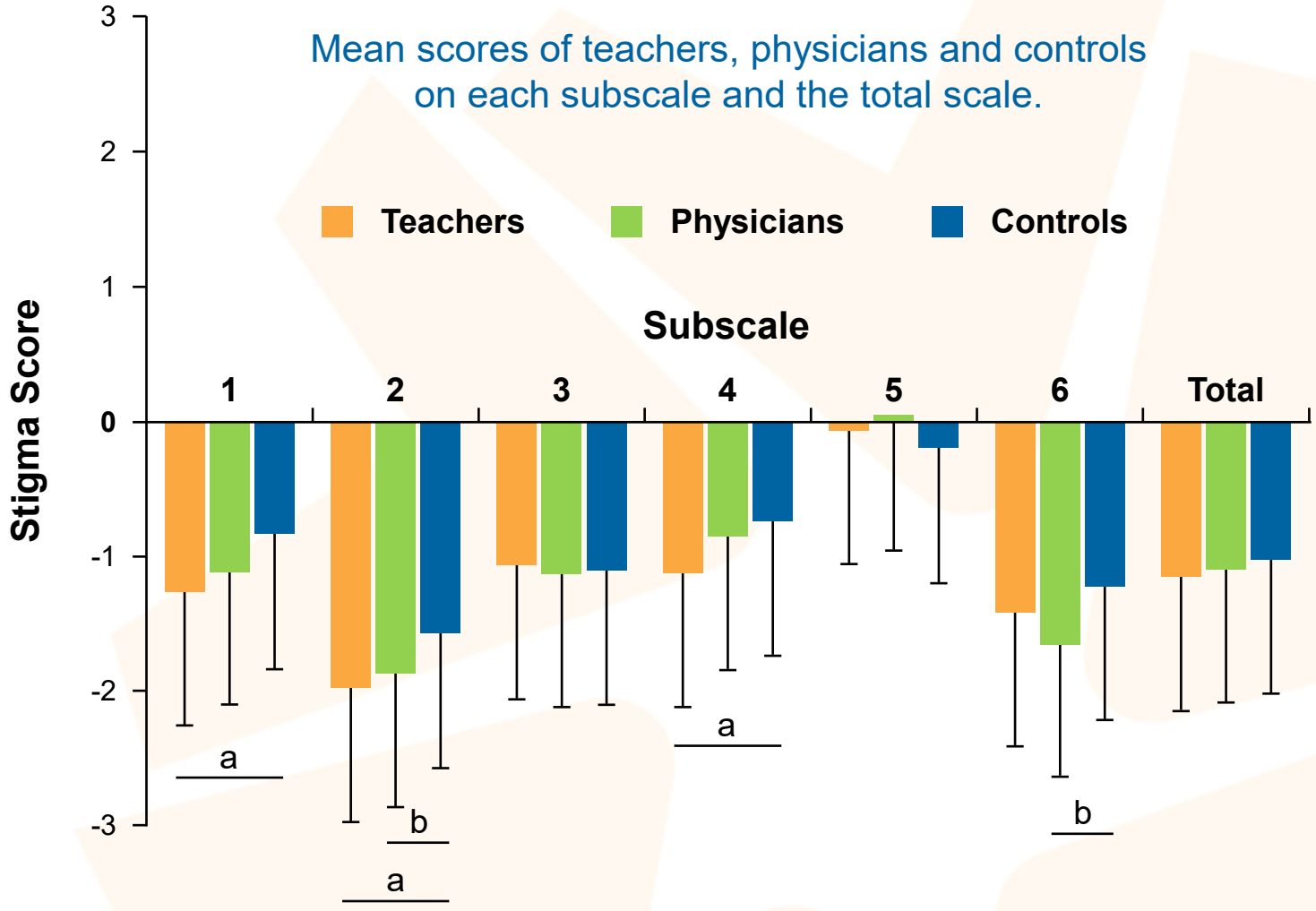
Masuch TV, et al. ADHD Attention Deficit and Hyperactivity Disorders. 2019;11:211-220.

Stigmatization Towards Adults with ADHD

Subscales:

1. Reliability and Social Functioning;
2. Malingering and Misuse of Medication;
3. Ability to Take Responsibility;
4. Norm-violating and Externalizing Behavior;
5. Consequences of Diagnostic Disclosure;
6. Etiology ("Adults with ADHD do not engage enough in sports")

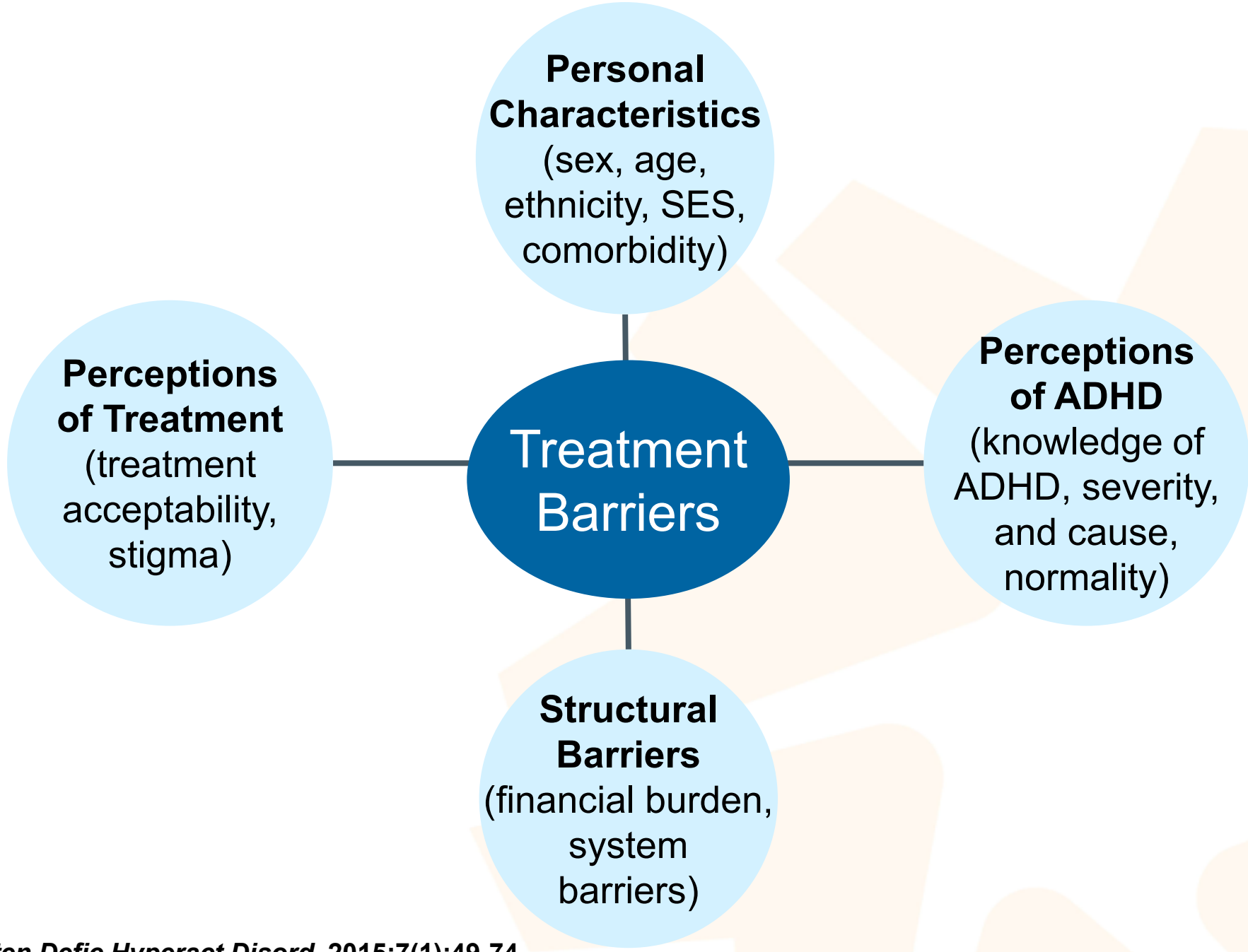
N=228 participants consisting of teachers, physicians, and control participants.



Fuermaier ABM, et al. 2012. PLOS ONE. 2012;7(12):e51755.

Tools in the “Toolbox”

- Get to know 1 or 2 long-acting MPHs, 1 or 2 long-acting AMPHs and 1 or 2 nonstimulants
- Consider onset and duration
- Titrate to optimal effect vs side effects
- Watch for breakthrough symptoms throughout the day, especially in mornings and evenings
- Use short-acting stimulants sparingly and avoid in
  - College students
  - Monotherapy in adults
  - When concerned about abuse, misuse or diversion



Corkum P, et al. *Atten Defic Hyperact Disord*. 2015;7(1):49-74.

Barriers to Medication Adherence

- Suboptimal/inadequate response
- Adverse effects: physical/psychological
- Inconvenience / effortful demands of taking medication regularly / multiple dosing
- Financial expense / insurance policy limits
- Availability of medications / supply issues
- Forgetfulness / disorganization / executive functioning skills deficits
- Oppositional behavior/ defiance / testing limits / autonomy
- Negative attitudes about medications
- Demoralization, defeatism, hopelessness
- Social stigma / self-stigma

Rostain AL. Improving Treatment Adherence of Patients with ADHD. Presented at: CADDRA 13th Annual Meeting; October 29, 2017; Quebec City, Canada.

Strategies for Improving Treatment Adherence

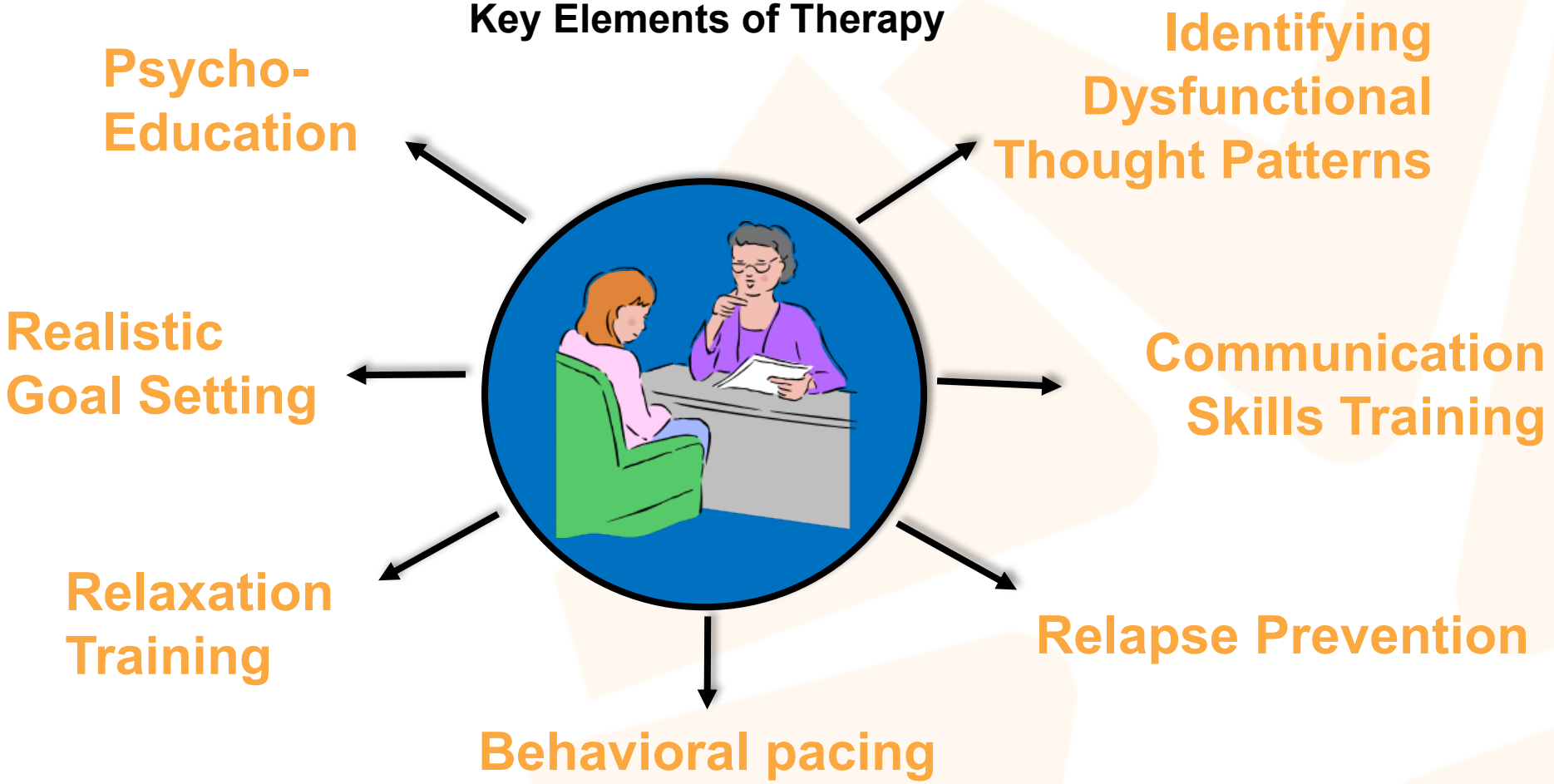
- Enhancing clinician-patient communication / alliance-building
  - Creating a collaborative framework for working together on “issues”
  - Remaining nonjudgmental, compassionate, and hopeful about change
- Defining realistic goals, expectations, and time frame for treatment
  - Picking best treatment options to meet patient’s/family’s priorities
- Addressing sources of treatment resistance (eg, adverse effects)
  - Staying continually aware of new or persistent barriers to adherence
  - Sustaining focus on patterns of avoidance underlying nonadherence (including misuse)
- Placing emphasis on managing transitions, especially youth and young adults
- Re-evaluating treatment practices to foster realistic outcomes

Adherence to treatment can be improved by establishing a close collaborative relationship, monitoring treatment efficacy, looking for problems with tolerability, and educating about risks of misuse

Rostain AL. Improving Treatment Adherence of Patients with ADHD. Presented at: CADDRA 13th Annual Meeting; October 29, 2017; Quebec City, Canada.

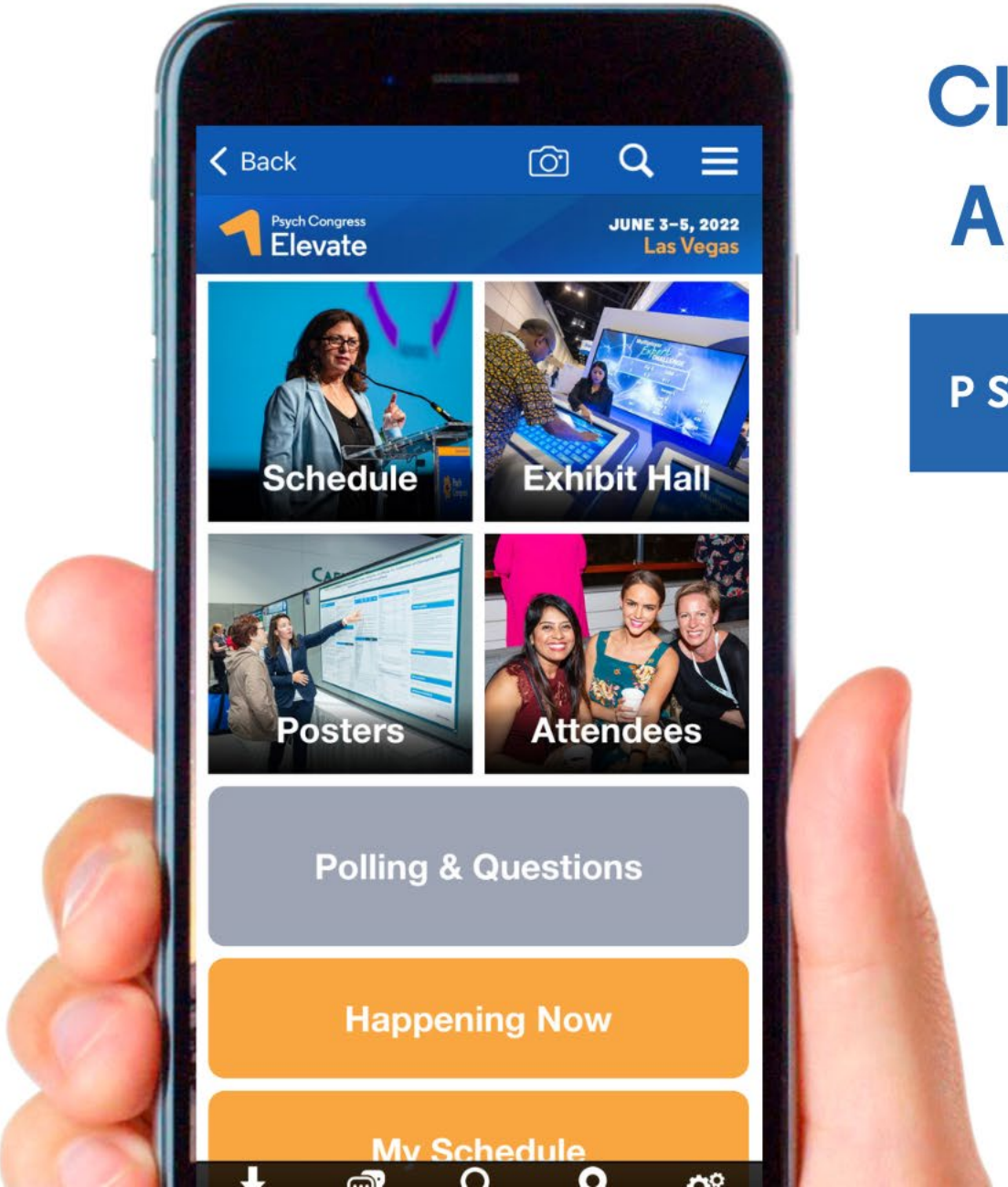
Breaking Down Stigma and Misperceptions

Key Elements of Therapy



Video Vignette #2

Considering Treatment after Non-pharmacological Approaches



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