

# Complex, Comorbid and Connected

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# Faculty Disclosure

## **Dr. Greg Mattingly:**

**Consultant** – AbbVie, Acadia, Akilli, Alkermes, Angelini, Axsome, Aytu, Biogen, BMS, Boehringer Ingelheim, Cerevel, Compass, Corium, Eisai, Ironshore, Intracellular, Johnson & Johnson, Liva Nova, Lumos Labs, Lundbeck, Manus, Neurocrine, Noven, Otsuka, Redax, Relmada, Revibe, Roche, Sage, Sirona, Sky Therapeutics, Sunovion, Supernus, Takeda, Teva, Tris Pharma;

**Research** – AbbVie, Acadia, Alkermes, Akilli, Alto Therapeutics, Autobahn, Avanir, Axsome, Boehringer Ingelheim, Cingulate, Click Therapeutics, Compass, Corium, Emalex, Idorsia, Intracellular, Johnson & Johnson, Karuna, Lumos Labs, Medgenics, Neumora, Neurocrine, NLS Pharma, Redax, Relmada, Roche, Sage, Sirtsei, Sumitomo, Sunovion, Supernus, Takeda, Teva;

**Speakers Bureau** – AbbVie, Alkermes, Angelini, Axsome, BMS, Corium, Intracellular, Ironshore, Johnson & Johnson, Lundbeck, Neurocrine, Noven, Otsuka, Supernus, Teva, Tris Pharma.

# Genetics of ADHD and Its Comorbidities: The Aspen Grove Phenomenon



# **New Updates from the CDC**

## **Age of ADHD Diagnosis Among US Adults**

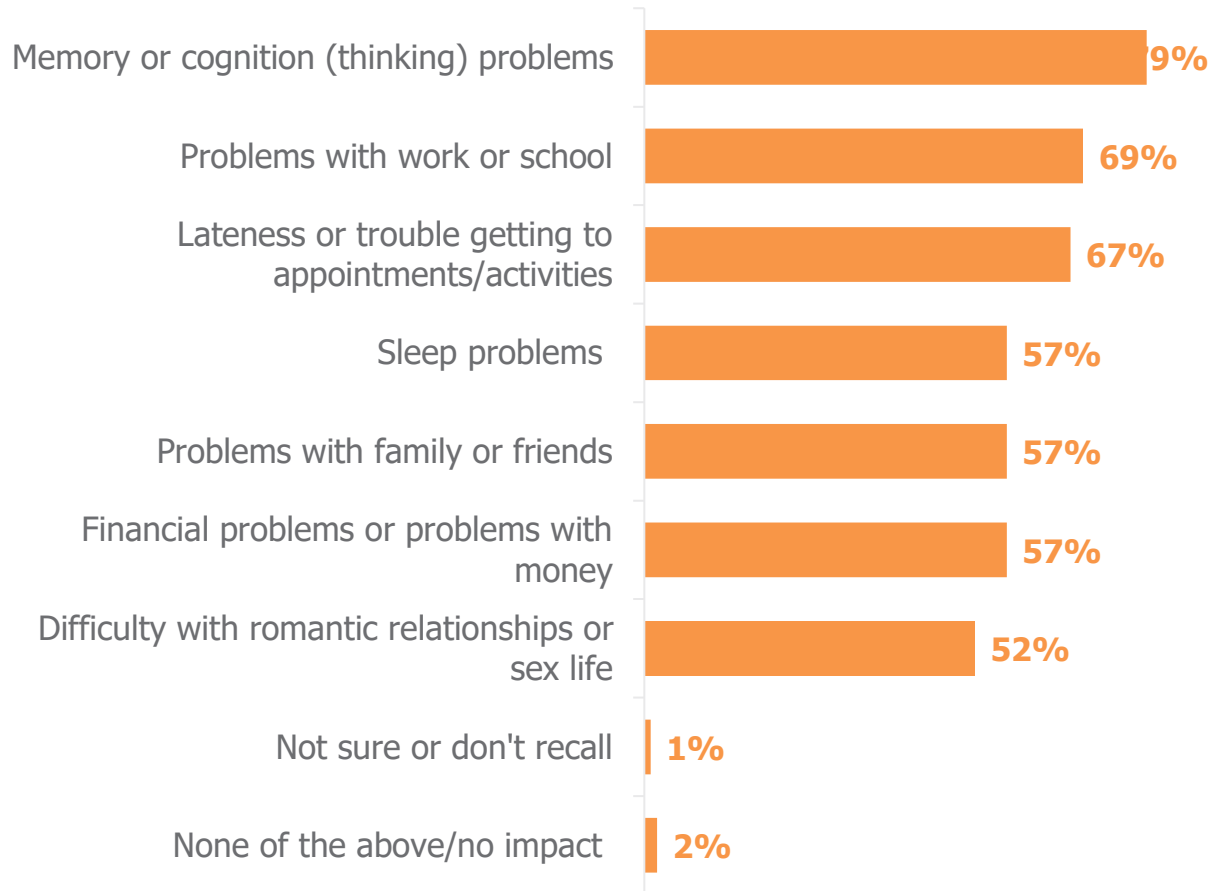
- **>50% of all ADHD Adults Diagnosed in Adulthood**
- **45% of men diagnosed < 12 yo ( 25% of women)**
- **61% of women diagnosed in adulthood ( 40% of men)**
- **9% of all ADHD adults diagnosed >45 years of age**
  - **8 % of adult ADHD men**
  - **11% of adult ADHD women**

**Staley SB et al. MMWR Morb Mortal Wkly Rep. 2024;73(40).  
Mattingly G & Childress A. J Clin Psychiatry October 2024;85(4):24.**

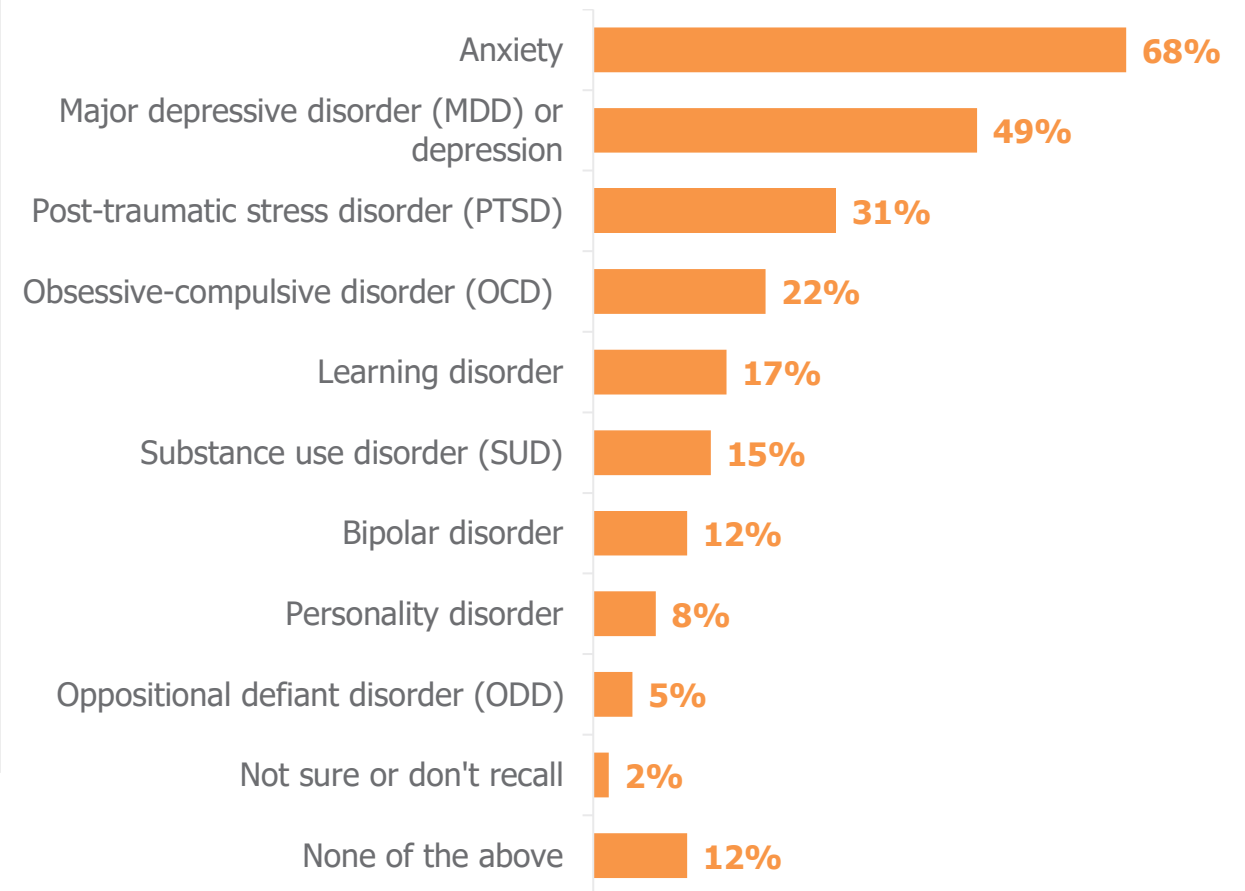
# Impact of ADHD and Additional Conditions

## APSARD, CHADD and Medscape Survey

How has quality of life been impacted for you/the person who is living with ADHD? (Select all that apply)



In addition to ADHD, which of the following conditions have you/the person you care for also been diagnosed with? (Select all that apply)



Medscape 2024, NASEM Report 2024

<https://nap.nationalacademies.org/read/27770/chapter/1><https://doi.org/10.17226/27770>

# Not Just ADHD

Most commonly complex and comorbid.

- 8.7X Risk for Bipolar Disorder
- 5X Risk for Anxiety Disorder
- 4.6X Risk for Substance Use Disorders
- 4X Risk for Major Depression
- Also increase rates of trauma, binge eating, disordered sleeping and other physical and emotional health conditions

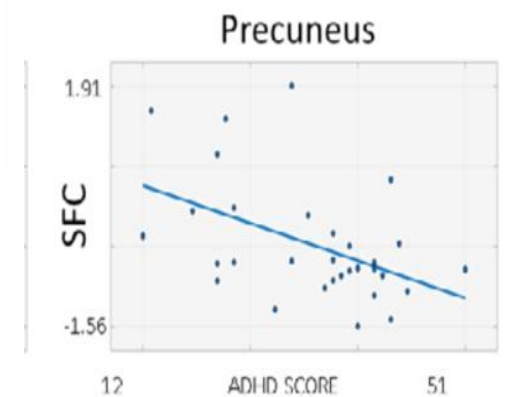
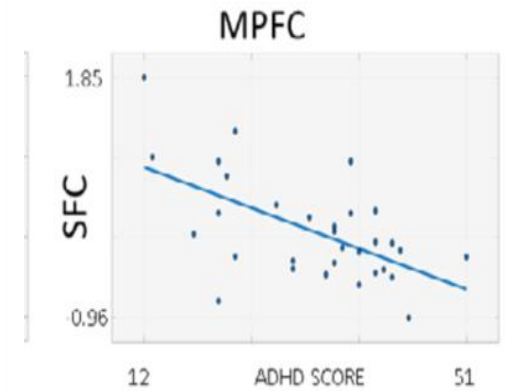
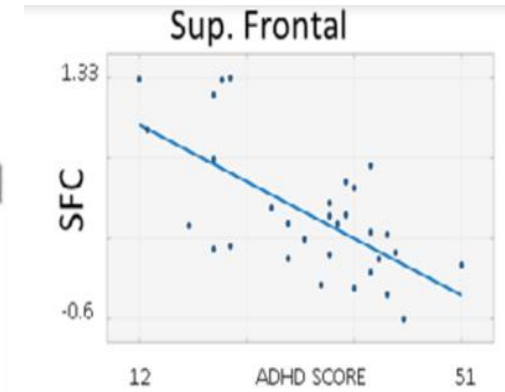
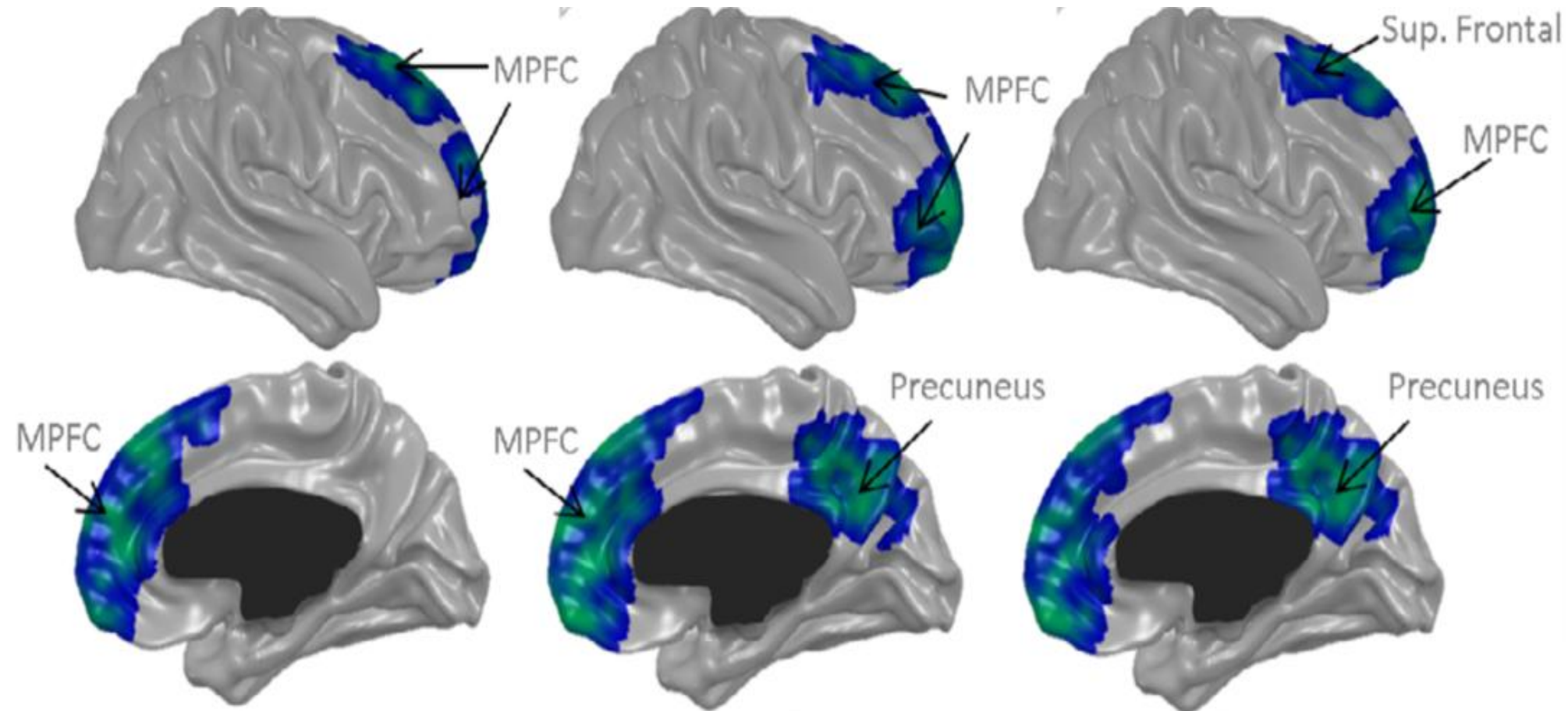
*Individualization of attention-deficit/hyperactivity disorder treatment: pharmacotherapy considerations by age and co-occurring conditions.*  
Mattingly GW et al. *CNS Spectr.* 2021;26(3):202–221.

# Why Do We See Elevated Comorbidity in ADHD?

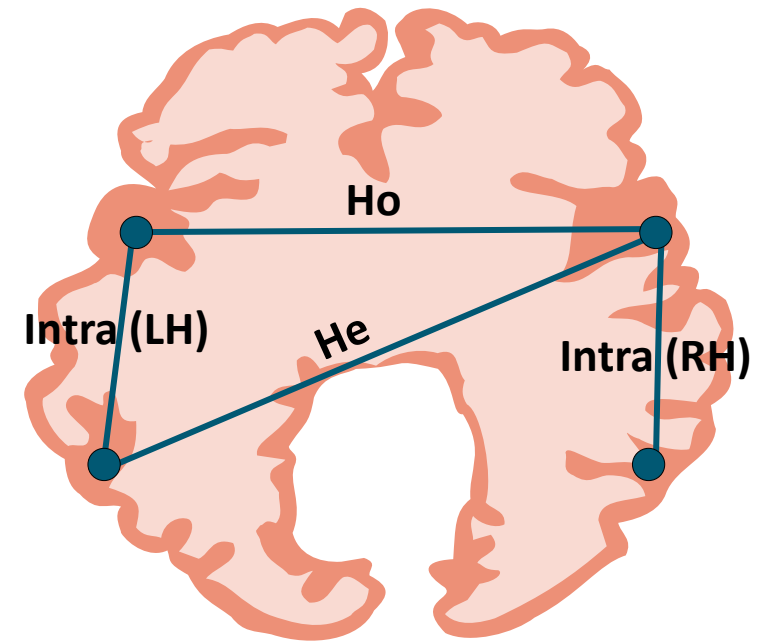
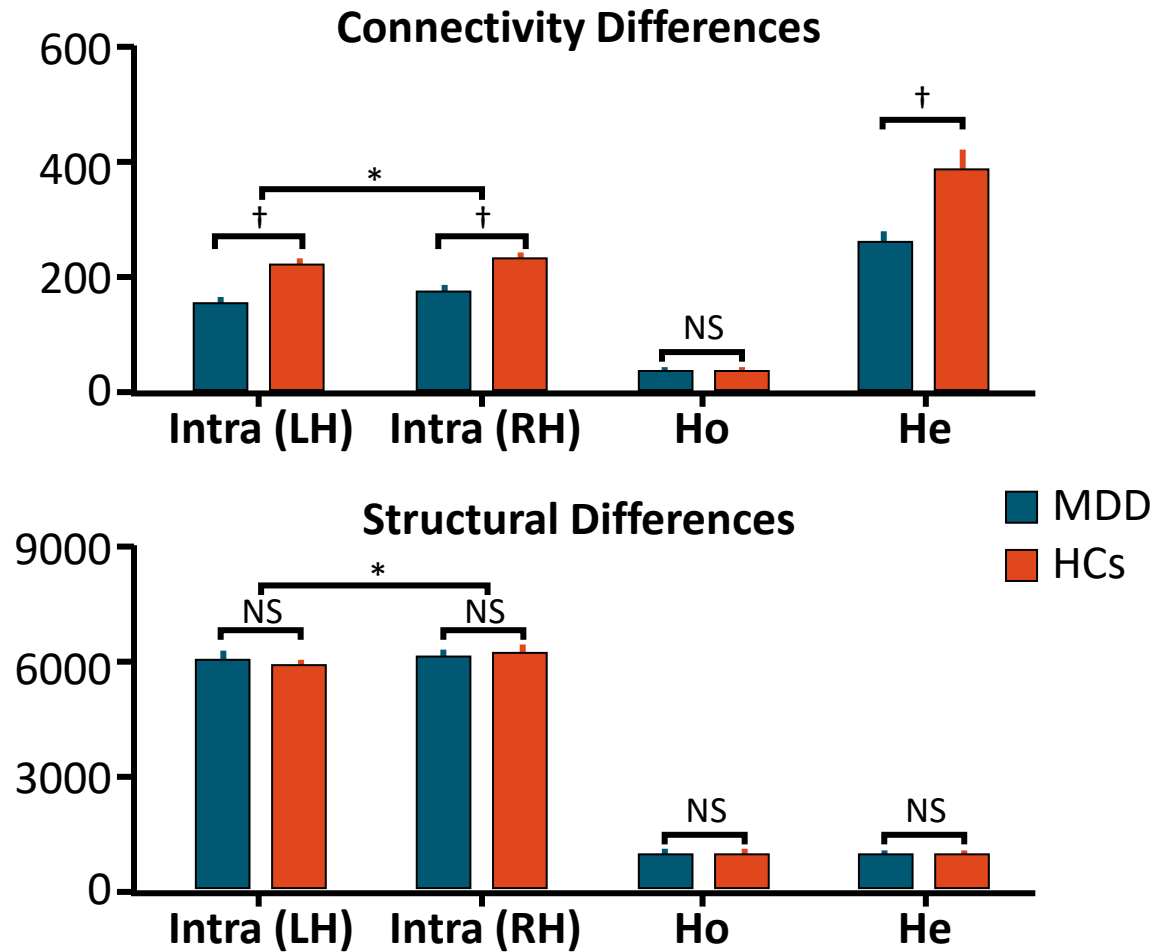
- Shared Genetics
- Stress Diathesis
- Shared Symptoms
- Shared Neural Mechanisms

# ADHD, Neural Connectivity and Resilience

# Decreased Functional Connectivity In Adult ADHD



# Impaired “Connectivity” in Depression



## Connecton types:

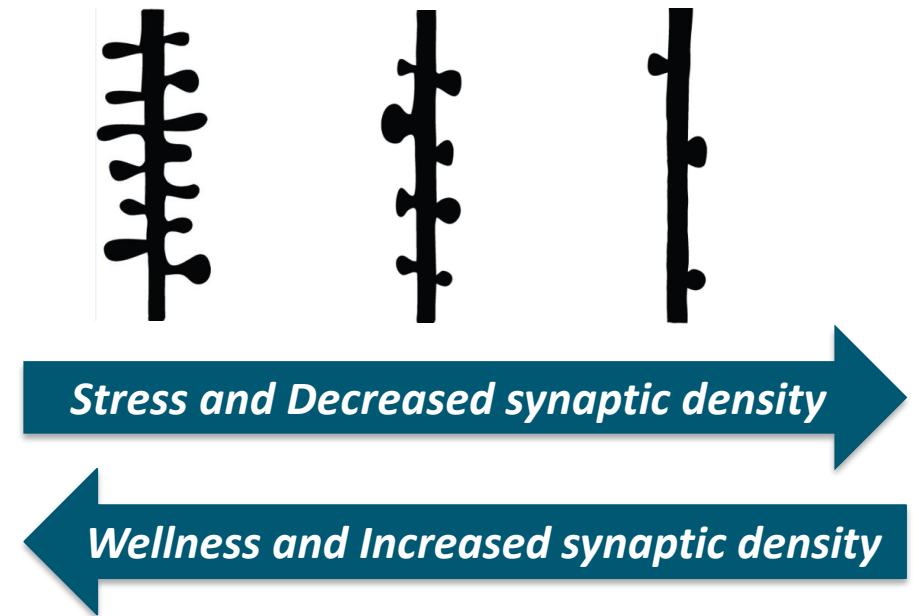
- Interhemispheric (Intra)
- Interhemispheric homotopic (Ho)
- Interhemispheric heterotopic (He)

\* $P < .01$ ; † $P < .001$

Jiang et al. Transl Psychiatry. 2019;9:136.

# Neuroplasticity, Neural Connectivity and Resilience

- **BDNF** is a neurotrophin that is needed for healthy **neuroplasticity** and reduced expression has been implicated in the pathophysiology of depression<sup>1-4</sup>
- **Impaired connectivity** leaves the brain **less resilient** and more likely to decompensate in response to stress<sup>8</sup>
- Days spent depressed decreases neural connectivity
- **Untreated adult ADHD** and symptom severity is associated with **impaired connectivity**



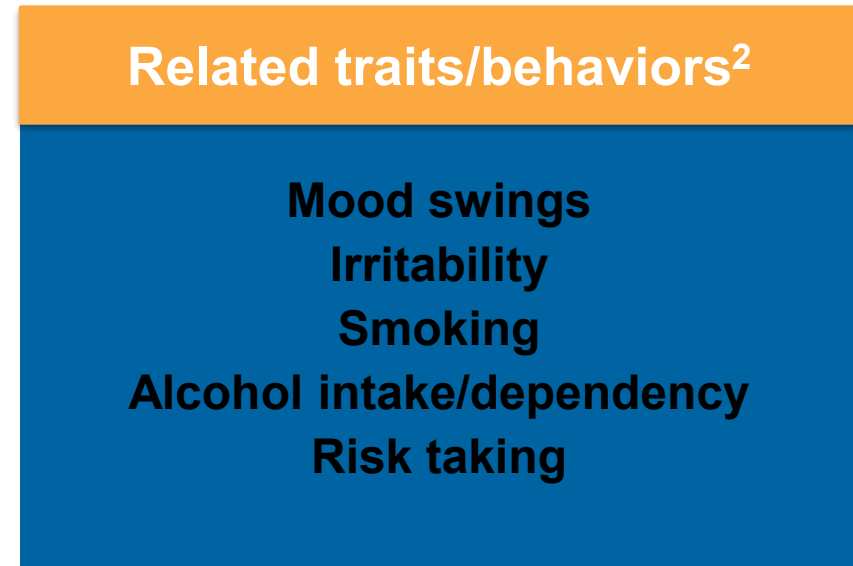
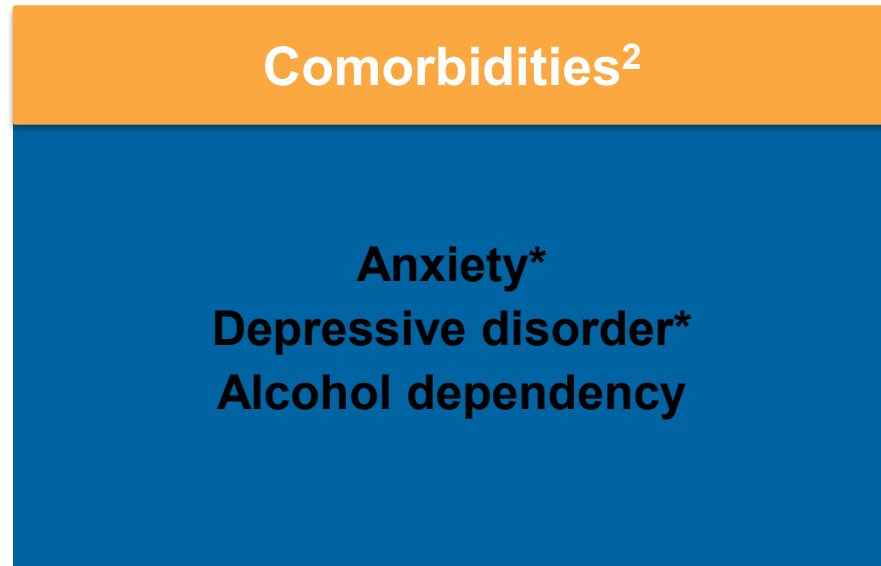
Individual synaptic connections are constantly being remodeled as a result of experience, emotional processing, learning, memory, and stress<sup>5-8</sup>

1. Dean et al. Asian J Psychiatr. 2017;27:101. 2. Monteleone et al. Bipolar Disord. 2008;10:95.  
3. Taliáz et al. Mol Psychiatry. 2010;15:80. 4. Castrén. JAMA Psychiatry. 2013;70:983. 5. Miller et al. Biol Psychiatry. 2009;65:732.  
6. Sanacora et al. Neuropharmacology. 2012;62:63. 7. Holtmaat et al. Nat Rev Neurosci. 2009;10:647. 8. Malhi & Mattingly. Transl Psychiatry. 2019 Nov 26;9(1):316.

# Polygenetic Risk and Epigenetics

# ADHD and Comorbidities Share Common Genetic Factors

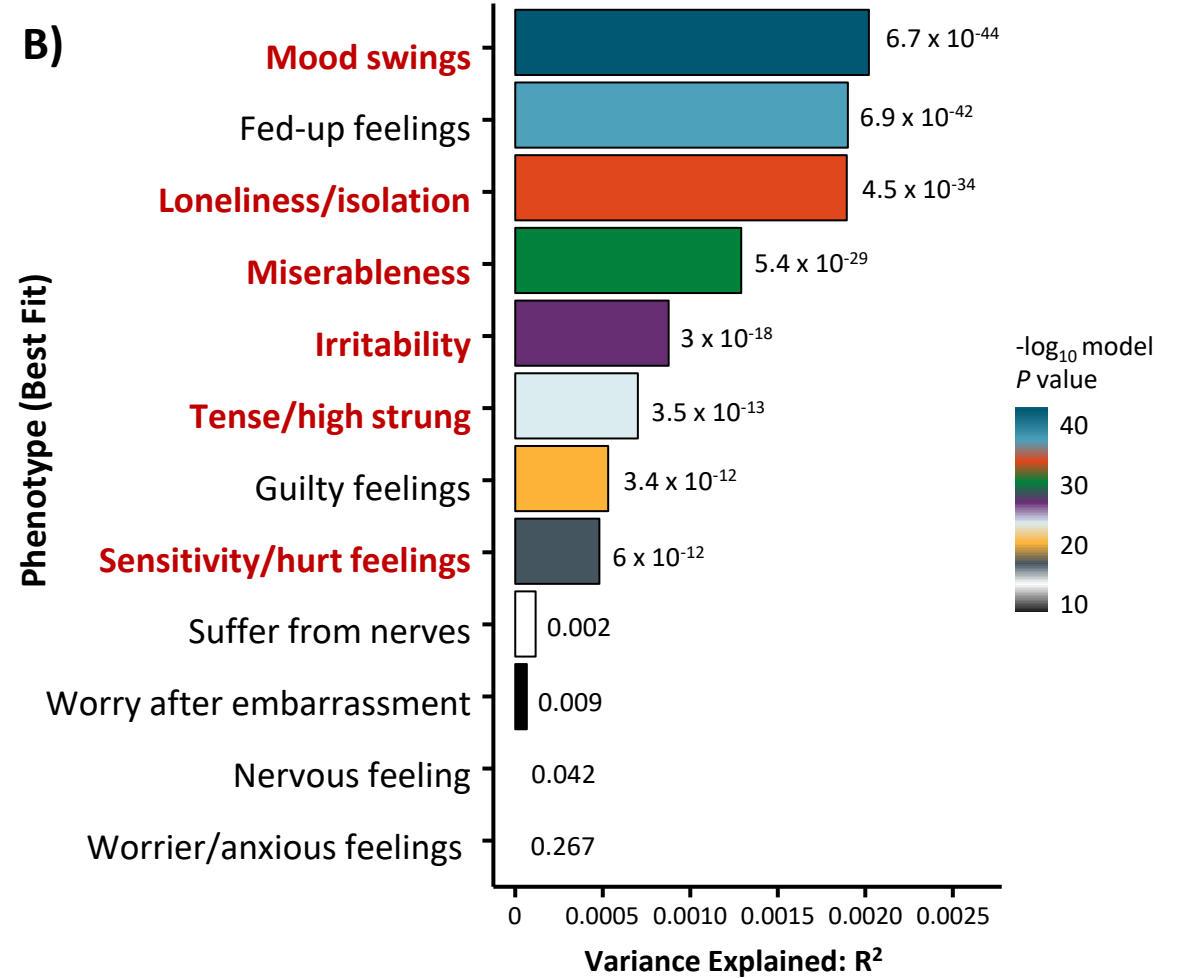
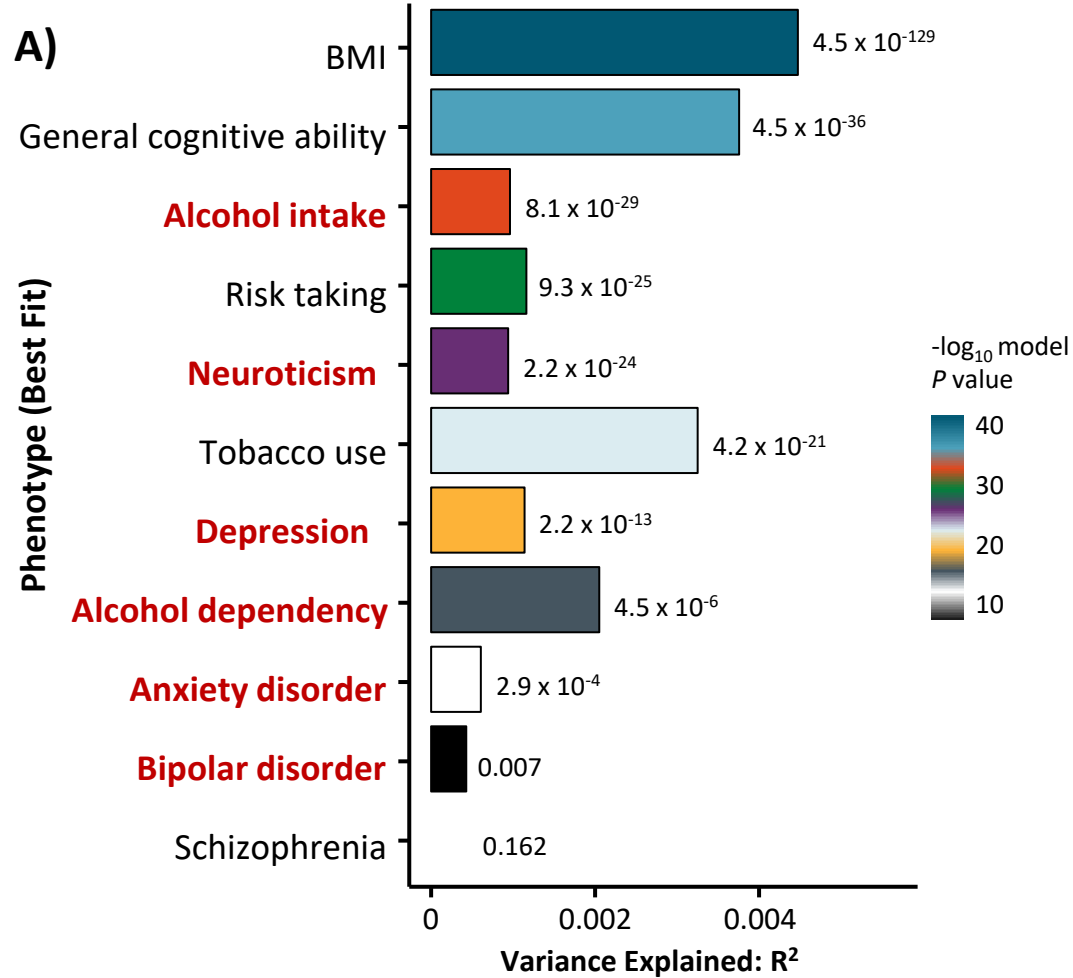
- ADHD has a high level of heritability (~74%-80%)<sup>1</sup>
- Data suggest that there are common genetic factors between ADHD and comorbidities and related traits/behaviors<sup>2</sup>



\*The 2 most commonly observed ADHD comorbidities.<sup>3</sup>

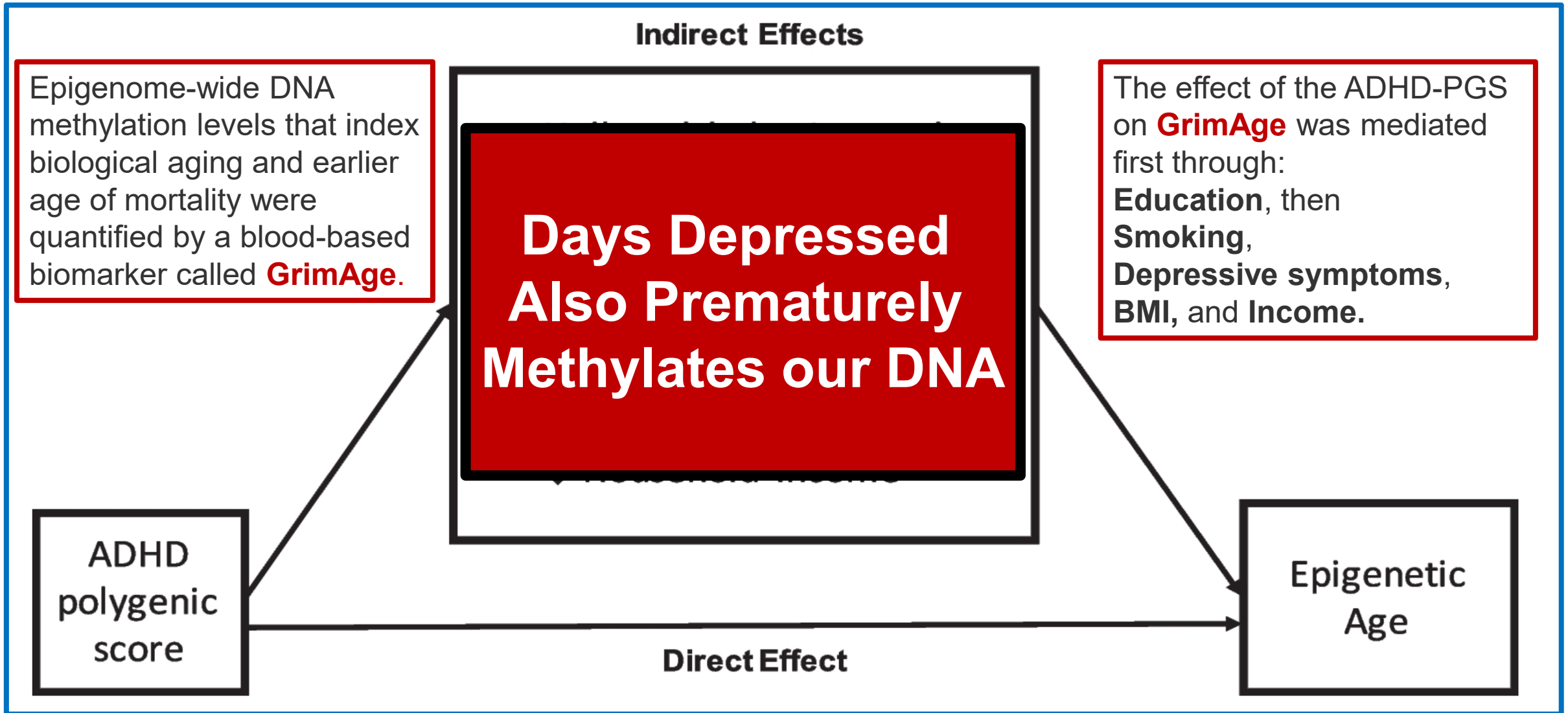
1. Faraone SV, Larsson H. *Mol Psychiatry*. 2019;24(4):562-575.
2. Du Rietz E et al. *Biol Psychiatry Cogn Neurosci Neuroimaging*. 2018;3(7):635-643.
3. Chung W et al. *JAMA Network Open*. 2019;2(11):e1914344.

# Polygenic Risk for ADHD and Associated Traits



Target phenotypes (A) and items on the neuroticism scale (B). Values displayed next to each bar represent the  $P$  value for significance for the most predictive models.

# ADHD Polygenic Burden Associates with Older Epigenetic Age



# Overlapping Diagnostic Symptoms

# Overlapping Symptoms of ADHD and Comorbidities

ADHD Symptoms							ADHD-related symptoms
Mood disorders	Hyperactivity		Impulsivity		Inattention		
	Excessive talking	Restlessness/agitation	Racing thoughts	Impulsive behaviours	Difficulty concentrating	Decreased attention	Mood swings /anger outbursts
MDD		✓			✓	✓	
Conduct disorders		✓		✓			✓
Bipolar disorder (hypomania)	✓	✓	✓	✓	✓	✓	✓
Anxiety		✓			✓	✓	✓
SUD	✓	✓		✓	✓		
Sleep disorders		✓			✓	✓	

# Which Mental Health Conditions Have Cognitive Dysfunction?

	Attention and/or Vigilance	Working Memory	Executive Function	Episodic Memory	Semantic Memory	Visual Memory	Verbal Memory	Procedural Memory	Processing Speed
Major Depression	+(+)	++	++	+++	+	+	+(+)	+	++(+)
Bipolar Disorder	++(+)	++	++	++	+	+	++	0	++
Schizophrenia	+++	+++	+++	+++	++	+(+)	+++	+	++
Autism Spectrum Disorder	+++	+	+++	++	+	+	+(+)	0/+	+++
ADHD	+++	++	+++	0/+	+	++	++	+	++
OCD	+++ (↑)	+(+)	++	+	0/+	+	0/+	++	++
PTSD	+++ (↑)	+(+)	+(+)	++	+	+	++(+)	0	+
Panic Disorder	+++ (↑)	+	0/+	+	0/+	0/+	+	0	++
GAD	+	+	0	0	+	+	+	0	0
Parkinson Disease	++	++(+)	++	+	0/+	+	+	+++	+++
Alzheimer Disease	+(+)	+(+)	+(+)	+++	+++	+++	++(+)	+	+

0, essentially absent; 0/+, poorly documented, ambiguous, mild and/or variable; +, consistently present but not pronounced; ++, a common, marked characteristic; +++, a core, severe and virtually universal characteristic of the disorder; ?, not clearly evaluated; ↑, increase

# 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	<b>1.56 (1.11–2.18)</b>
ADHD plus 1 comorbidity	73	57,575	12.68	<b>4.21 (3.27–5.42)</b>
ADHD plus 2 comorbidities	90	29,952	30.05	<b>8.57 (6.73–10.92)</b>
ADHD plus 3 comorbidities	73	14,146	51.60	<b>15.69 (12.08–20.37)</b>
ADHD plus ≥4 comorbidities	94	10,334	90.96	<b>29.29 (22.77–37.66)</b>
None of the above	3452	15,991,953	2.16	<b>1 [Reference]</b>

# 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



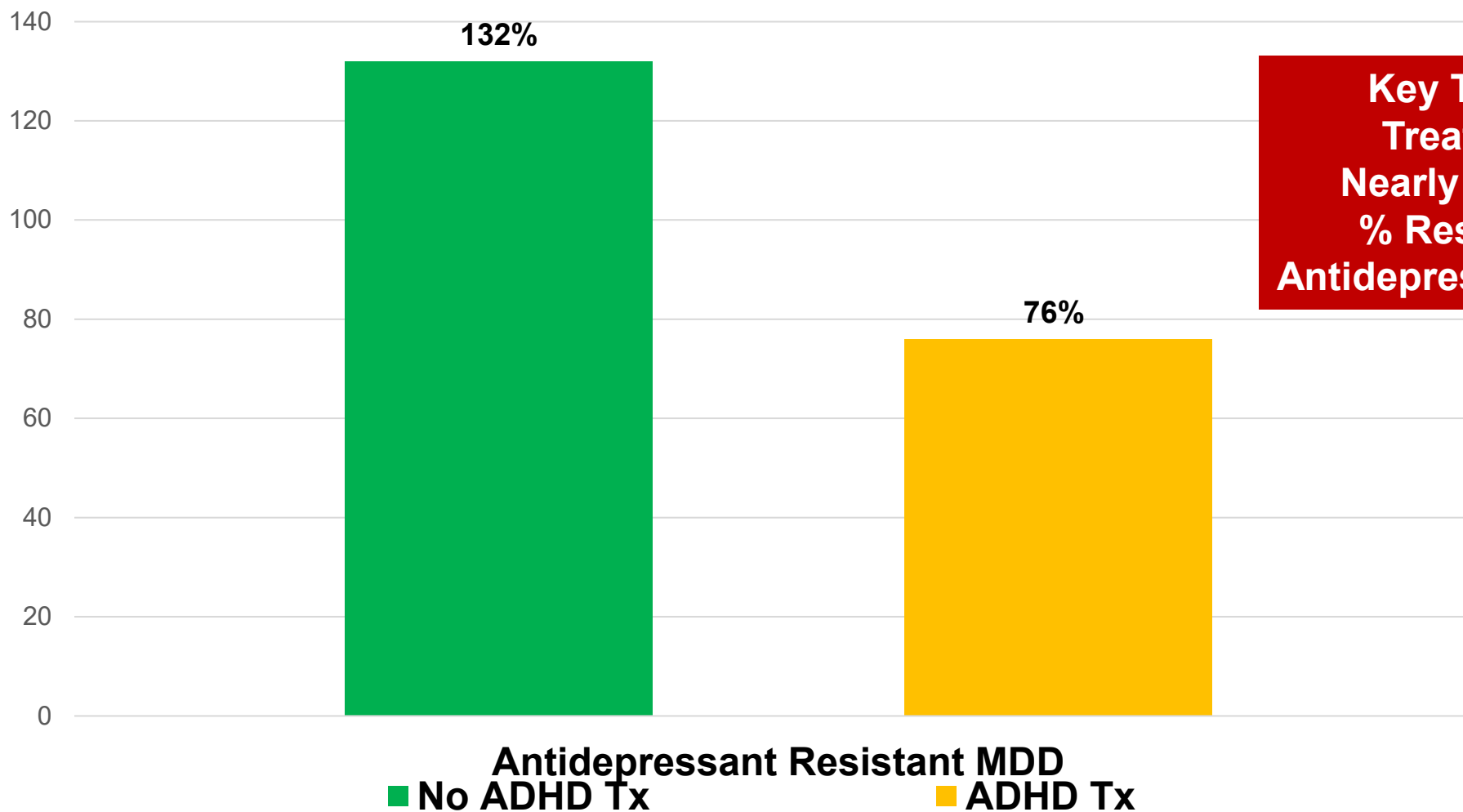
A Nationwide Study found that MDD/ADHD patients were twice as likely to be antidepressant nonresponders and nonresponse was cut in half when their ADHD was treated along with their MDD

MDD = major depressive disorder.

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

# Increased Antidepressant Resistance Among Patients With ADHD and MDD

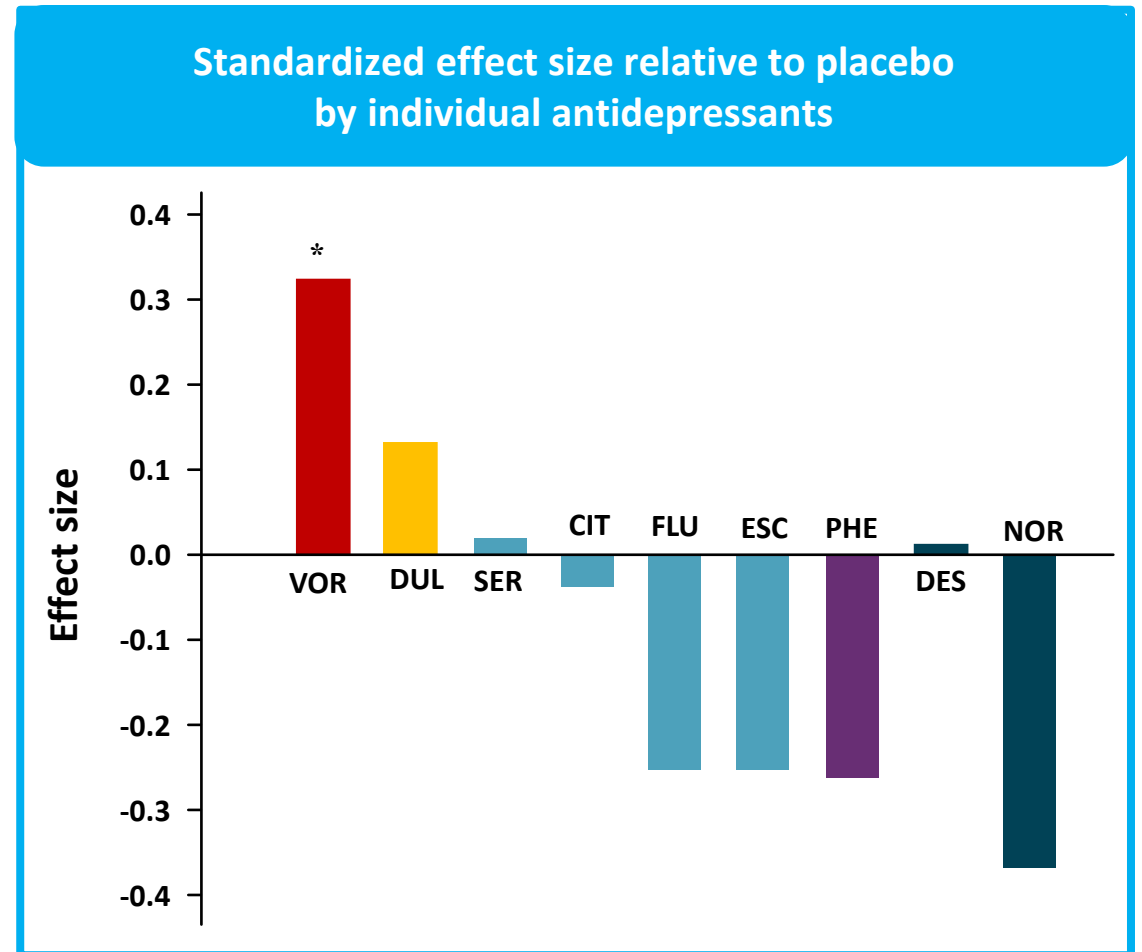
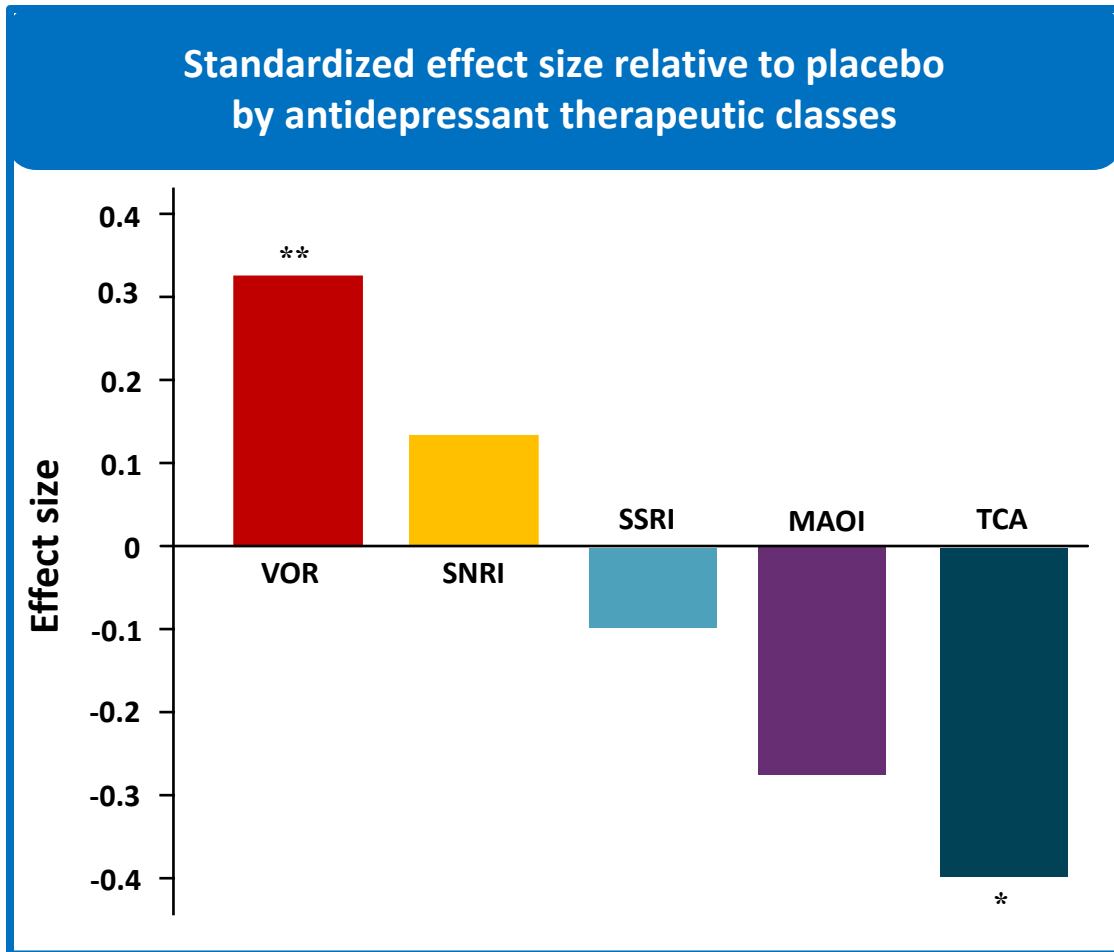
1,891 Patients with MDD and 1,891 Patients with MDD and ADHD



**Key Take Home:  
Treating ADHD  
Nearly Doubled the  
% Responders to  
Antidepressant Treatment**

# Comparing Effects of Antidepressants on Cognition

## Improvement in Processing Speed on DSST



DSST = Digit Symbol Substitution Test

Mattingly GW et al. *Postgraduate Medicine*. 2016;8:665. Baune BT, et al. *Int J Neuropsychopharmacol*. 2018;21:97.

Mattingly GW et al. *Front Psychiatry*. 2022 Mar 9;13:824831..

# Treatment Resistant Depression and ADHD

## Combining Glutamatergic Options with a Stimulant

- Esketamine- FDA Approved for Treatment Resistant Depression
  - Modulates NMDA Receptor
  - Increases Synaptic Glutamate and Neuroplasticity
  - Our clinic has done >6,000 esketamine treatments over the past 6 years
  - 54% of our esketamine patients have comorbid ADHD
- In the past 2 years we have also used increasing amounts of bupropion-dextromethorphan (*Auvelity*) for these comorbid patients

# How About Depression With Mixed Features?

## Depression with 3 or More Manic/Hypomanic Symptoms

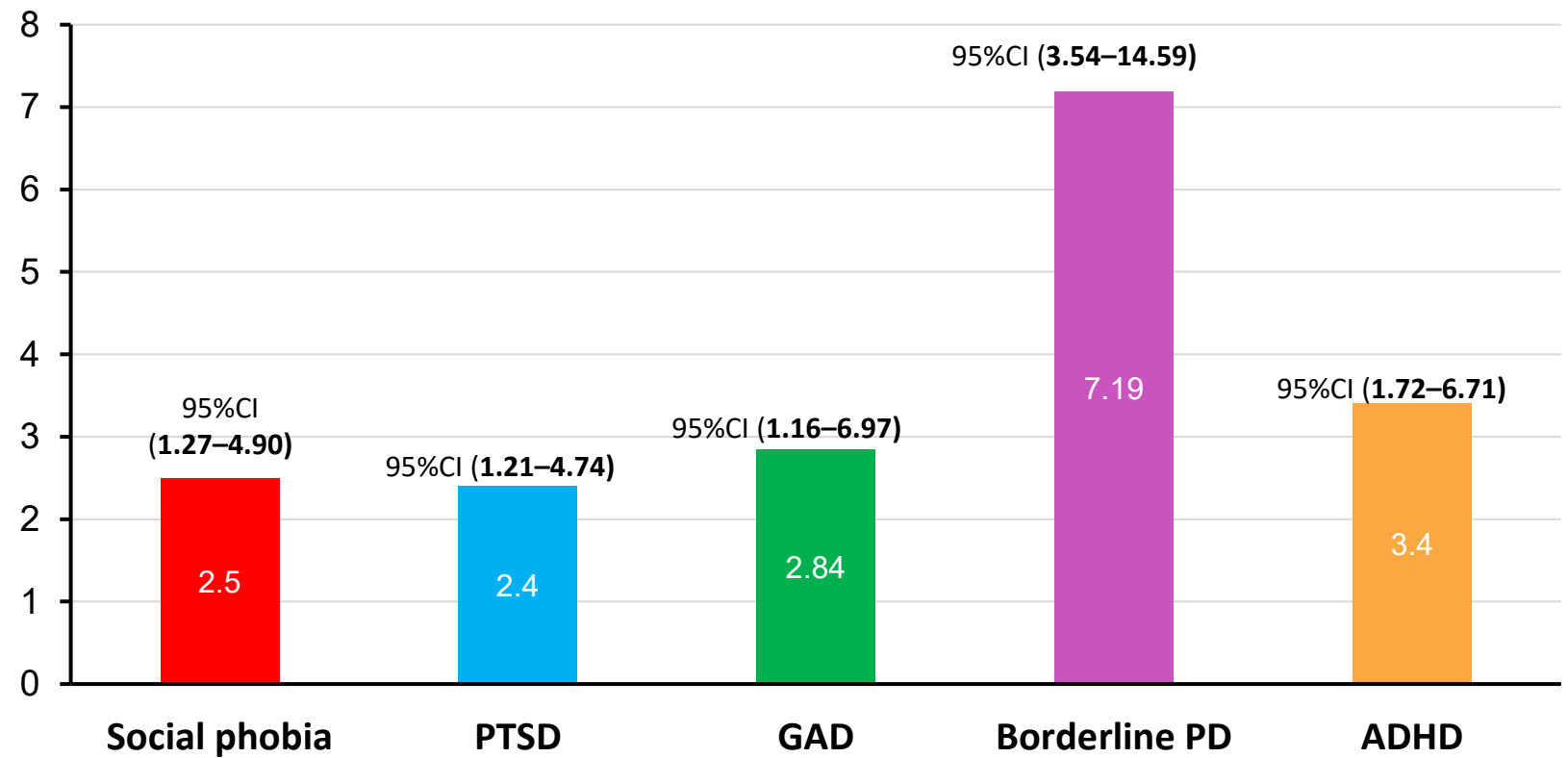
- 1) Elevated, expansive mood
- 2) Inflated self-esteem or grandiosity
- 3) More talkative or pressured speech
- 4) Flight of ideas or thoughts are racing
- 5) Increase in energy or goal-directed activity
- 6) Increased activities that have a high potential for painful consequences
- 7) Decreased need for sleep

# Depressed Patients With Mixed Features Have More Severe Course of Illness and More Psychiatric Comorbidities

N=459 psychiatric patients in a depressive episode were interviewed using DSM-5 Mixed Features Specifier Interview (DMSI). Patients with mixed features were:

- **More severely depressed**
- **Anxious and irritable**
- **More frequently attempted suicide**

Odds Ratio (OR) of comorbid disorder in depressed patients with mixed features vs. without



Abbreviations: CI, confidence interval; OR indicates odds ratio.  
Zimmerman, Mackin, 2024, *Bipolar Disorders*

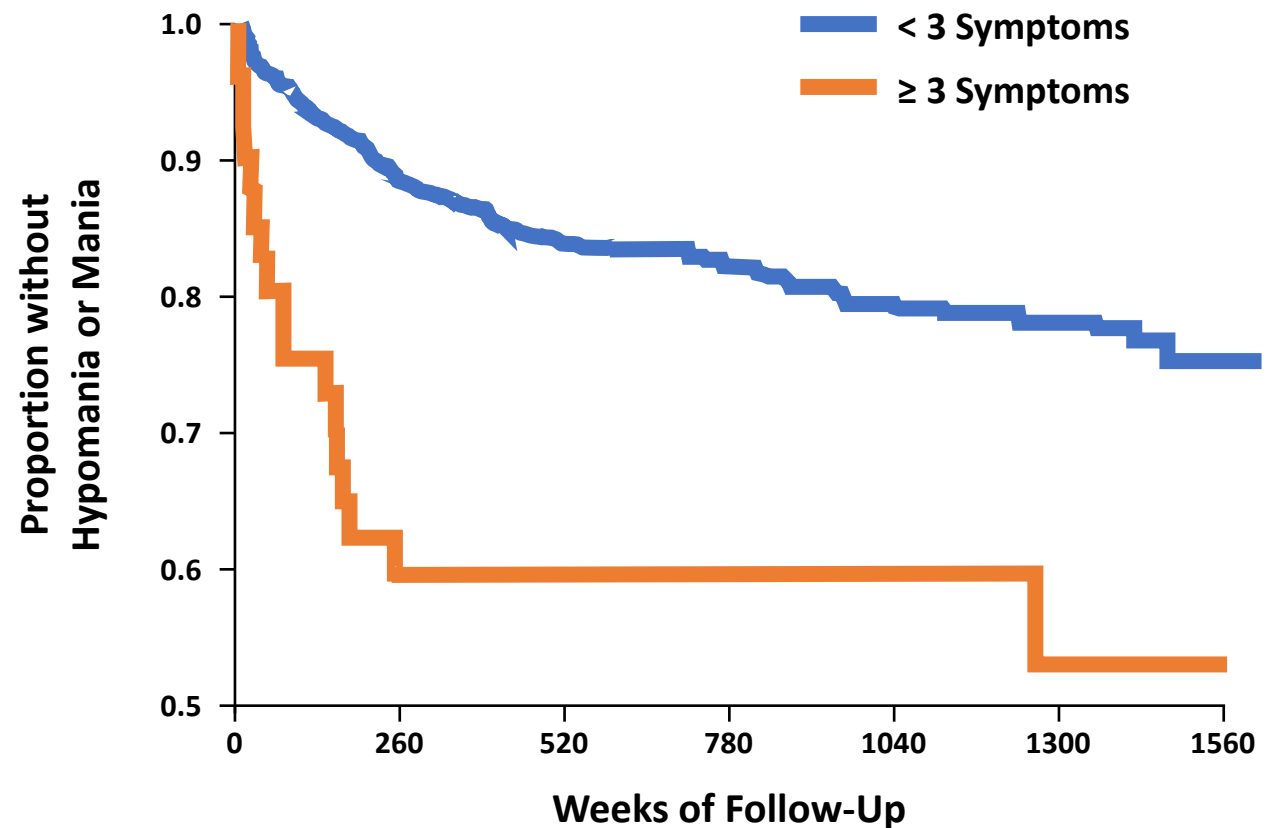
# Mixed Features Increase the Chance of Switch

National Institute of Mental Health Collaborative Depression Study

**550 MDD patients followed for 17.5 years**

- **19.6%** (N=108) experienced hypomania or mania
- Number of subthreshold hypomanic symptoms, presence of psychosis, and age at illness onset predicted progression to bipolar disorder

Decreased need for sleep, unusually high energy, and increased goal-directed activity were specifically implicated.

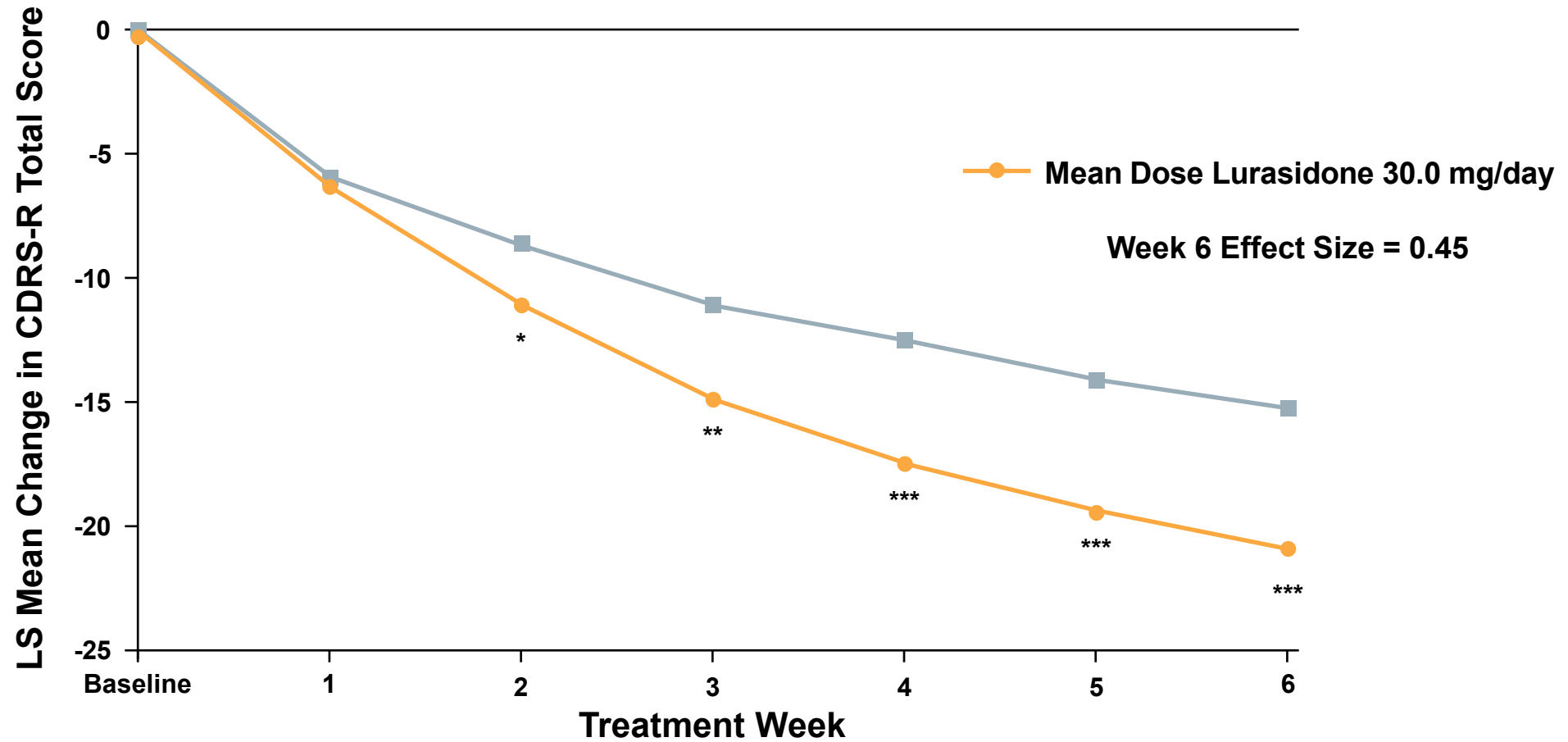


# 5 Atypical Antipsychotics Approved for Bipolar Depression Treatment

	Dose		Adverse Events
	Initial	Recommended	
Lurasidone	20-40 mg	20-120 mg	Akathisia, EPS, somnolence
Quetiapine / Quetiapine XR	50 mg	150-300 mg	Sedation, weight gain
Olanzapine/fluoxetine	6/25 mg	6/25-12/50 mg	Sedation, weight gain, appetite, metabolics
Cariprazine	1.5 mg	1.5-3 mg	Akathisia
Lumateperone	42 mg	42 mg	Somnolence

# Treatment of Pediatric Bipolar Depression with ADHD

# Lurasidone for Youth with BD: CDRS-R Total Score



CDRS-R = Children's Depression Rating Scale-Revised.

\* $P < .05$ . \*\* $P < .001$ . \*\*\* $P < .0001$ .

Goldman R, et al. American Academy of Child and Adolescent Psychiatry; October 22-27, 2018; Seattle, WA. Abstract 6.1; DelBello MP, et al. *J Amer Acad Child Adolesc Psychiatry*. 2017;56:1015-1025.

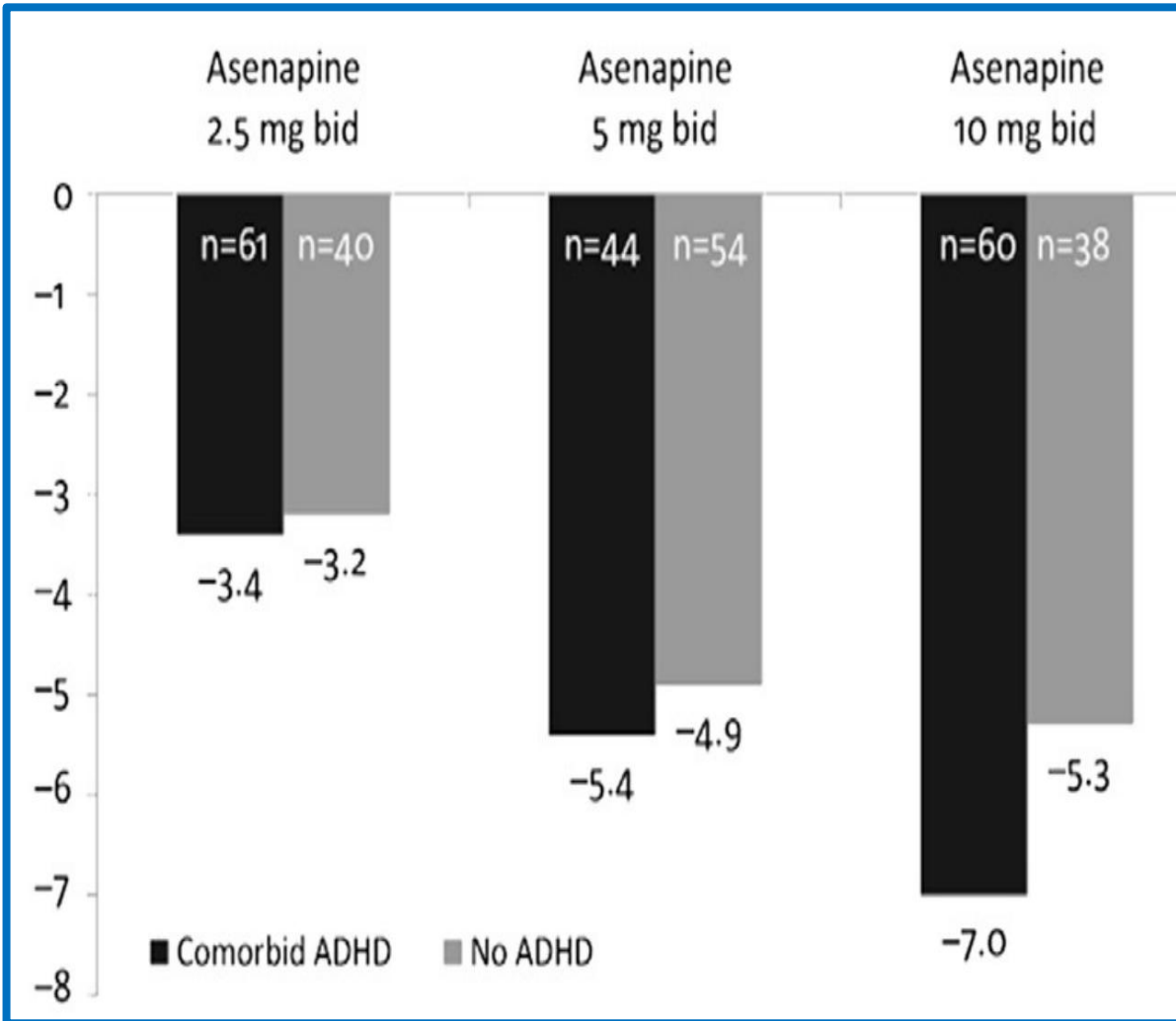
Characteristic	Lurasidone 20–80 mg/d (n = 173)		Placebo (n = 170)	
	n	%	n	%
Males	88	50.9	87	51.2
Females	85	49.1	83	48.8
Race				
White	134	77.5	125	73.5
Black/African-American	15	8.7	18	10.6
Asian	7	4.0	4	2.4
Other	17	9.8	23	13.5
Ethnicity: Hispanic/Latino	31	17.9	33	19.4
Region				
United States (US)	74	42.8	73	42.9
Non-US	99	57.2	97	57.1
Age group at screening				
10–14 y	88	50.9	85	50.0
15–17 y	85	49.1	85	50.0
Patients with $\geq 1$ hospitalization for bipolar depression	44	25.4	49	28.8
ADHD diagnosis	41	23.7	37	21.8
ADHD treated with stimulants	18	10.4	21	12.4

**Lurasidone for Pediatric Bipolar Depression**  
**24% with ADHD**  
**10% on stimulants**

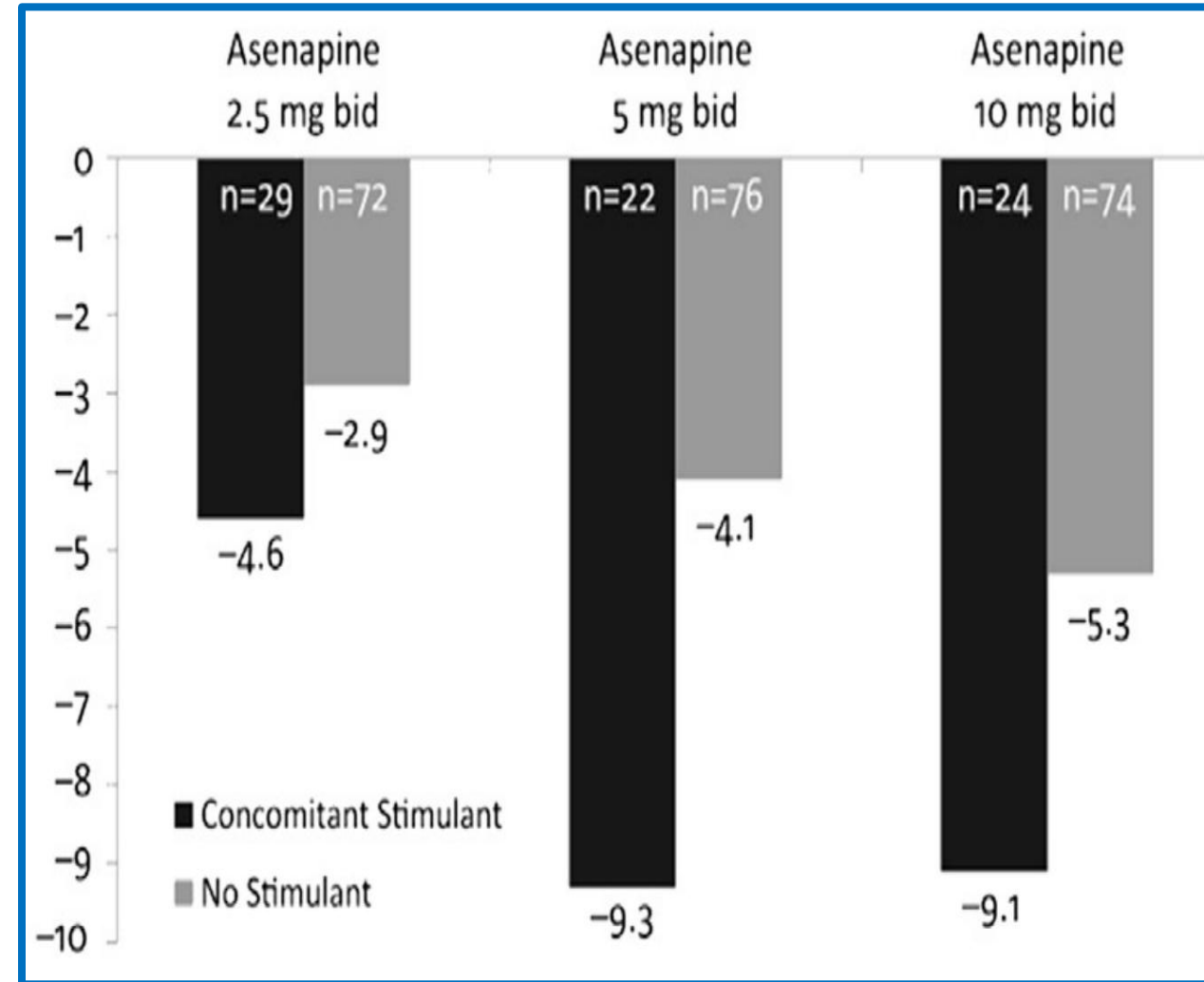
# Treatment of Pediatric Bipolar Mania with ADHD

# Pediatric Bipolar Mania and ADHD

Do Manic/ADHD Patients Have Similar Response?



Should We Avoid Stimulants in ADHD/Mania?



# 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**

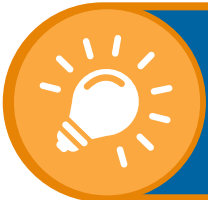
Within 6 months after treatment initiation, SA and NSSI events decreased significantly in terms of:

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

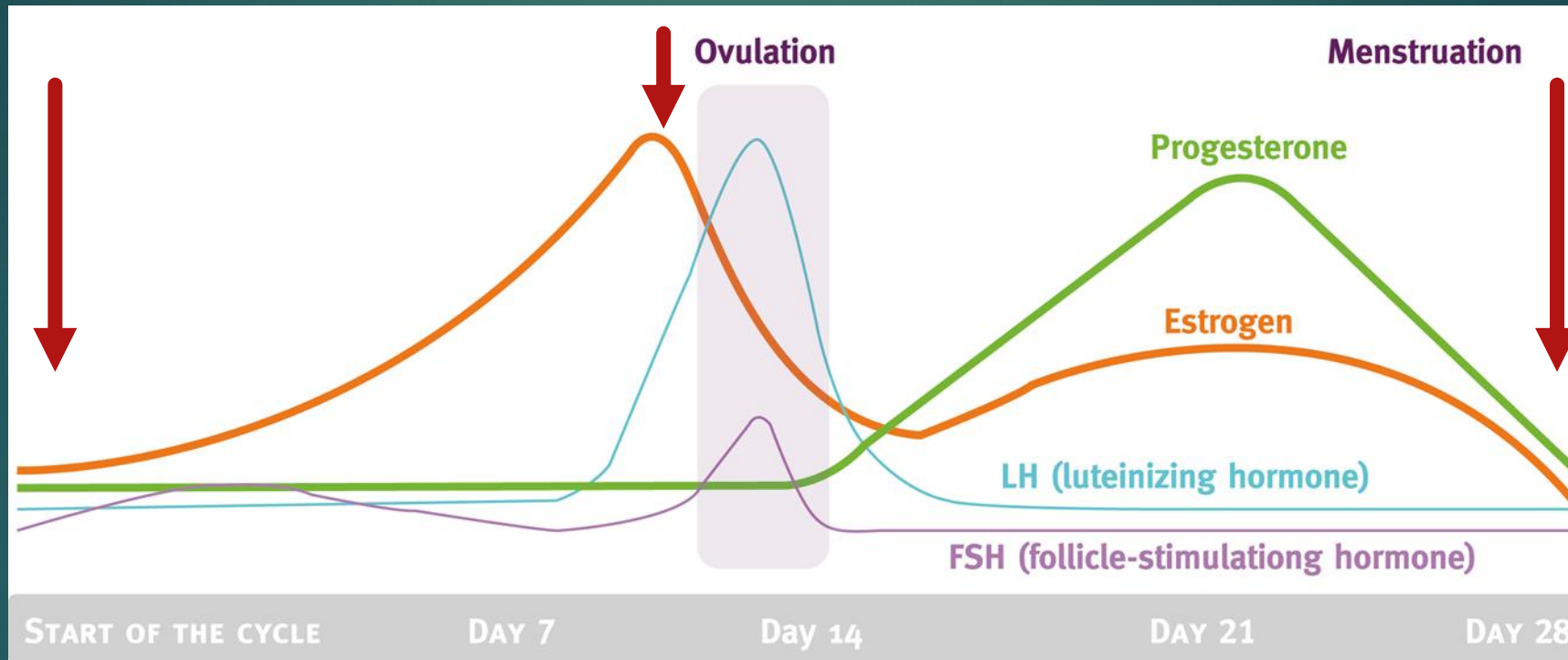
# Effects of Hormonal Fluctuations on Inattention and Impulsivity

**30-50% increase in ADHD Rx for 7 days**  
*Front. Psychiatry, December 2023.*

Inattention

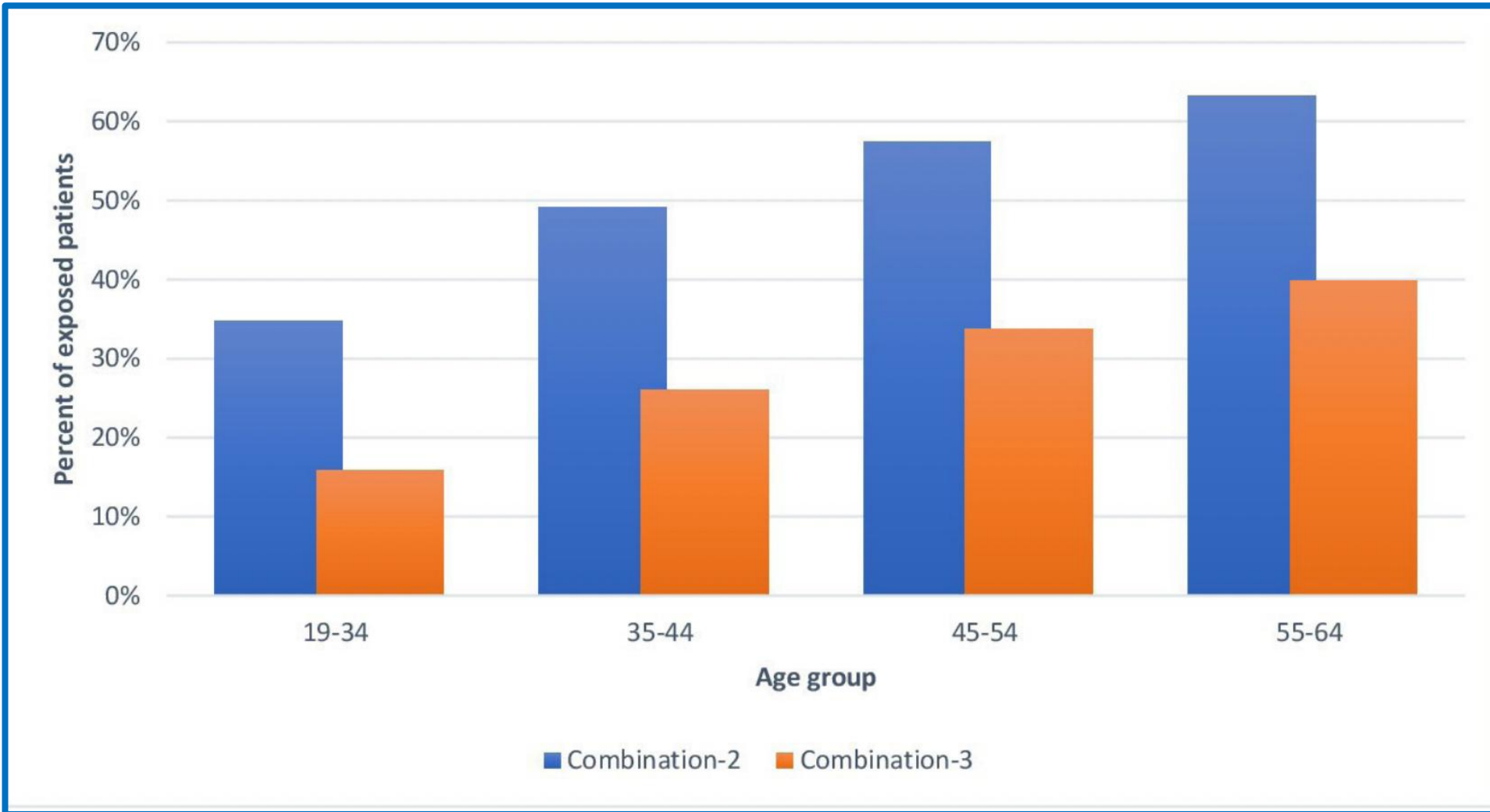
Impulsivity

Inattention



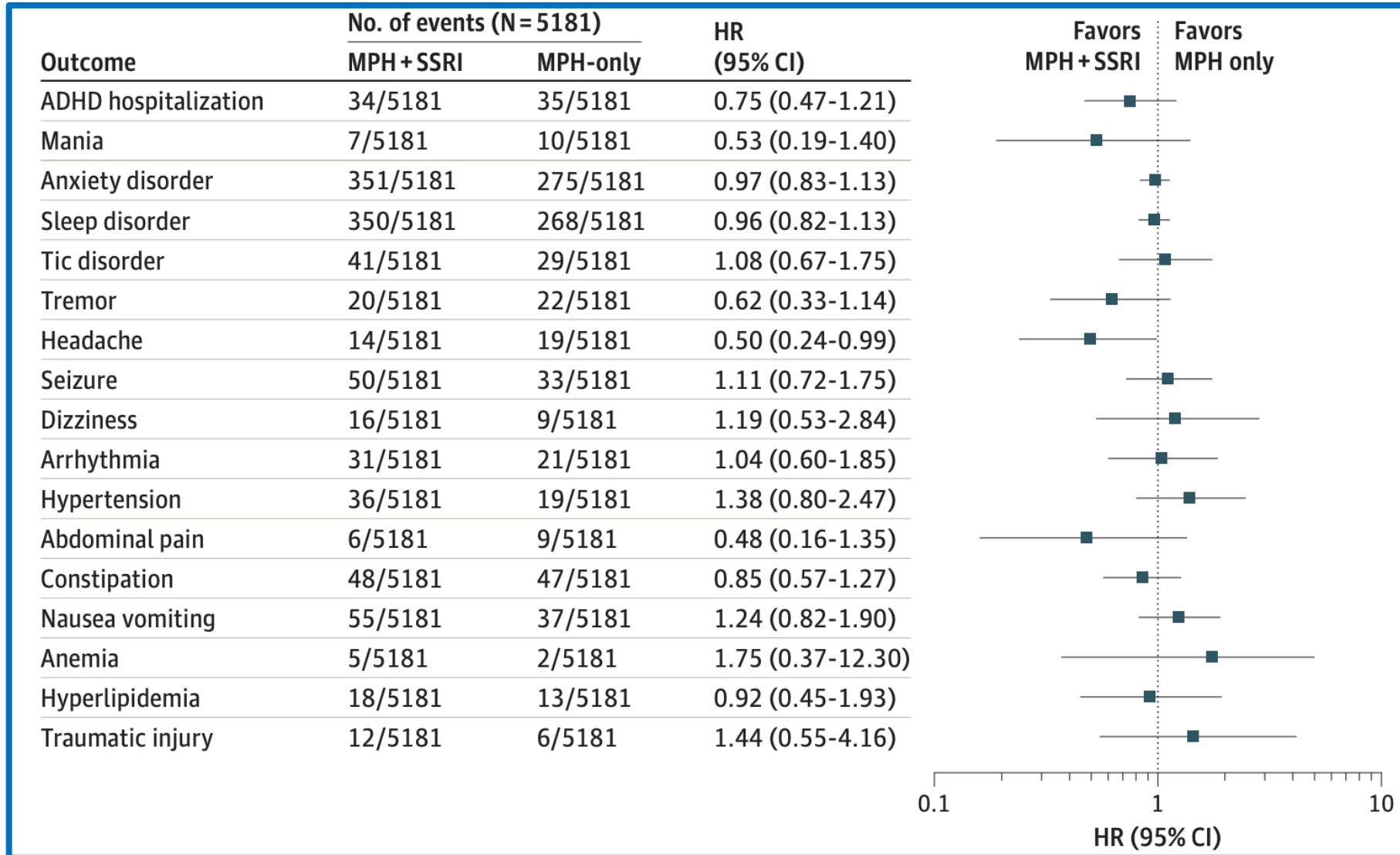
- ▶ Hormonal effects on ADHD across the menstrual cycle

# Prevalence of Combination Therapy With Stimulants by Age Group



# A Nationwide Cohort Study of Outcomes

## MPH vs MPH + SSRI (47%)



# What is the Most Common Medication to Combine With A Stimulant?

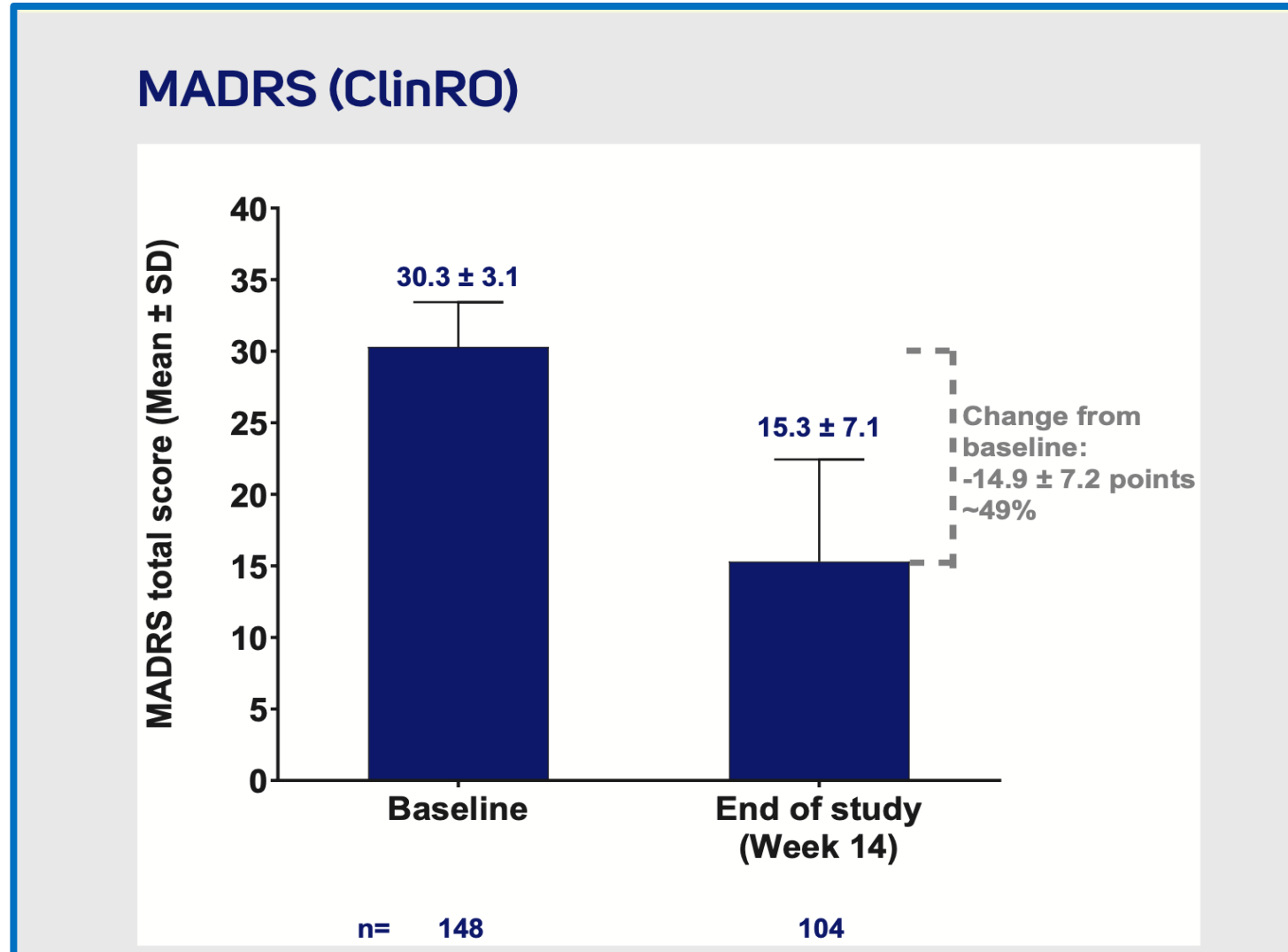
Drug class†	Prescriptions	Persons
	No (%)	No (%)*
Anticonvulsant	225 592 (10.3)	38 112 (13.8)
Antidepressant	987 582 (45.1)	131 485 (47.6)
Antipsychotic	143 611 (6.6)	22 650 (8.2)
Anxiolytic/sedative/ hypnotic	540 619 (24.7)	85 166 (30.8)
CNS other	75 613 (3.5)	14 558 (5.3)
Opioids other	48 257 (2.2)	11 322 (4.1)
Opioids Schedule II	149 368 (6.8)	42 713 (15.5)
Stimulant other	19 705 (0.9)	4 368 (1.6)

# Viloxazine ER for Adults with ADHD and Comorbid Mood and Anxiety Symptoms

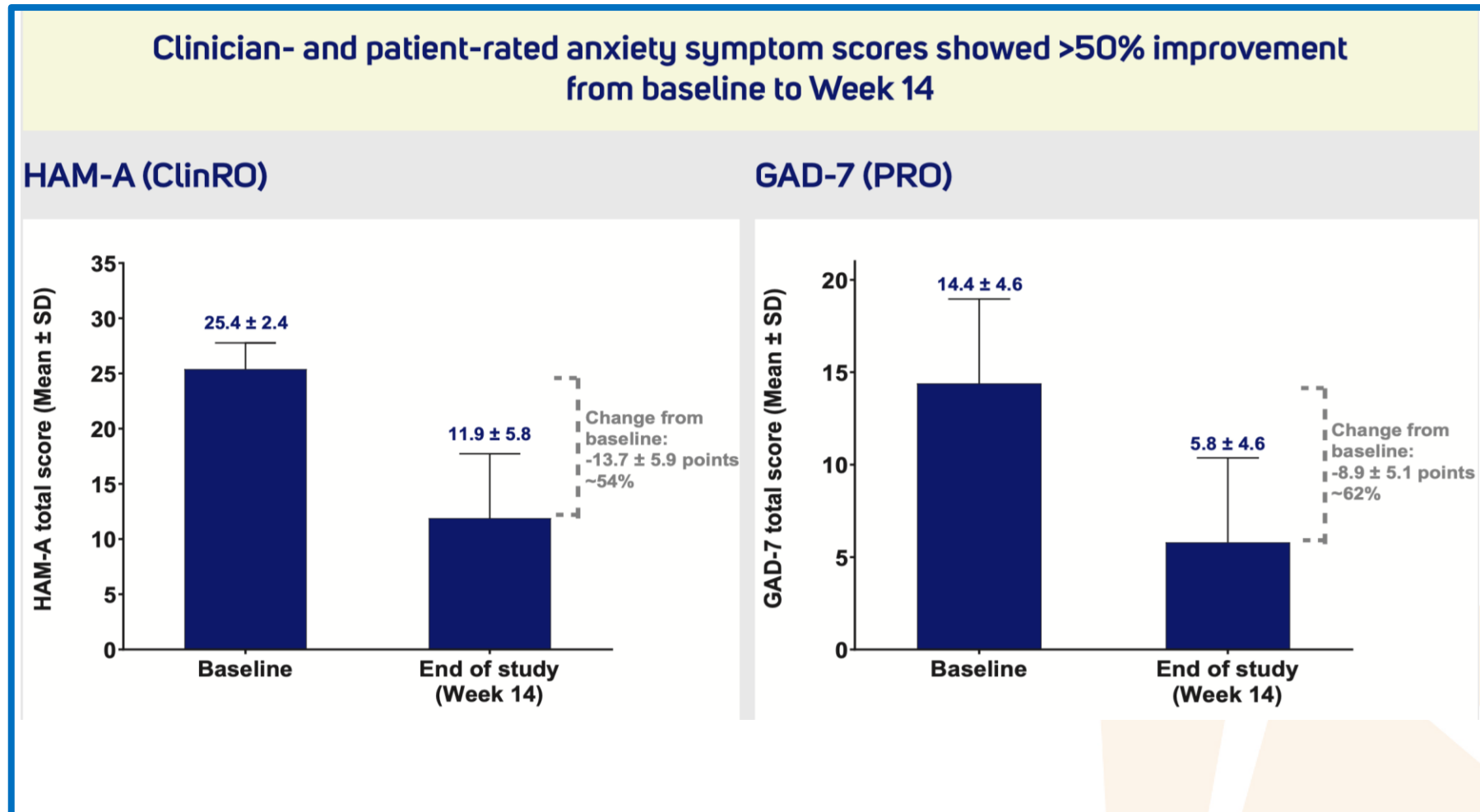
**> 50 % improvement in ADHD sx**

Safety population, N=161	
Age (years), mean $\pm$ SD	39.5 $\pm$ 10.6
Sex, female	75.2%
Race, white	79.5%
BMI (kg/m <sup>2</sup> ), mean $\pm$ SD	31.7 $\pm$ 9.0
College degree (2 or 4 year)	36.0%
Currently employed	72.1%
Married	37.9%
Total AISRS, mean $\pm$ SD	37.4 $\pm$ 6.5
Total MADRS, mean $\pm$ SD	30.3 $\pm$ 3.1
Total HAM-A, mean $\pm$ SD	25.4 $\pm$ 2.3
Total MADRS >22	100%
Total HAM-A >22	99.4%
Total MADRS >22 and HAM-A >22	99.4%

# Viloxazine ER Improvement in Depressive Symptoms in ADHD Patients



# Viloxazine ER Improvement in Anxiety in ADHD Patients



# “Anna”



## Anna

- 39 years old
- Working mother
- 2 kids
- **Meds:** SSRI for MDD

### Presenting Complaint

**“I’m taking my medicine but am just not right”**

### Clinical Results

- Patient Health Questionnaire (PHQ-9) = 18
- Generalized Anxiety Disorder 7 (GAD 7) = 12
- ADHD Rating Scale (ADHD-RS) = 32
- Mood Disorder Questionnaire (MDQ) = 4
- PTSD checklist for DSM-5 (PCL-5) = 10



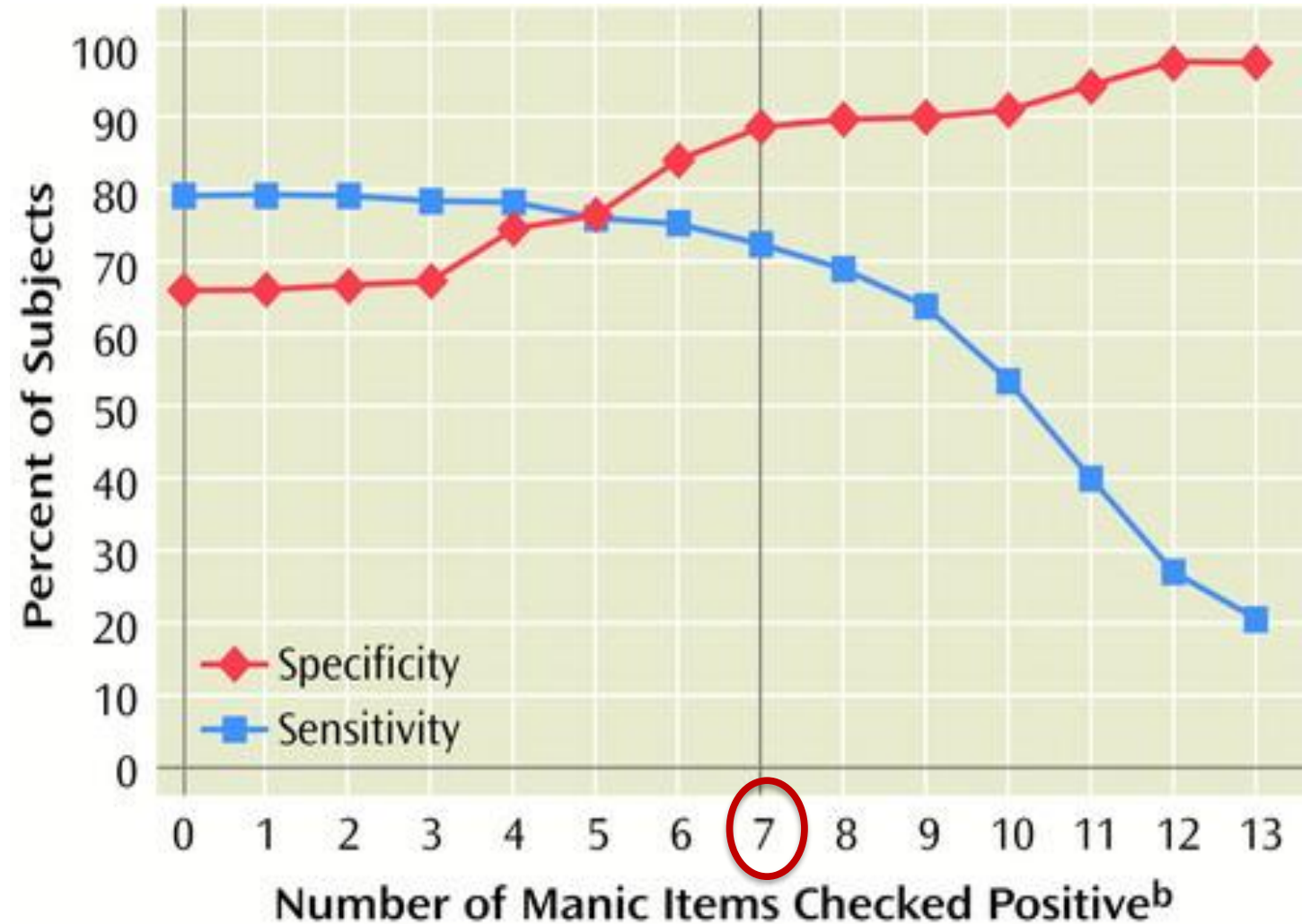
**What do you do next?**

# Mood Disorder Questionnaire (13 items)

## 7 or more screen +

**5 Psych Clinics**  
**198 pts**  
**73% Sensitivity**  
**90% Specificity**

**UT Family Med**  
**649 pts on MDD tx**  
**21.3% were MDQ+**  
**58% Sensitivity**  
**93% Specificity**



# PHQ-9 for Anna



**PHQ-9, GAD7,  
MDQ and PCL-5  
Downloadable  
Resources**

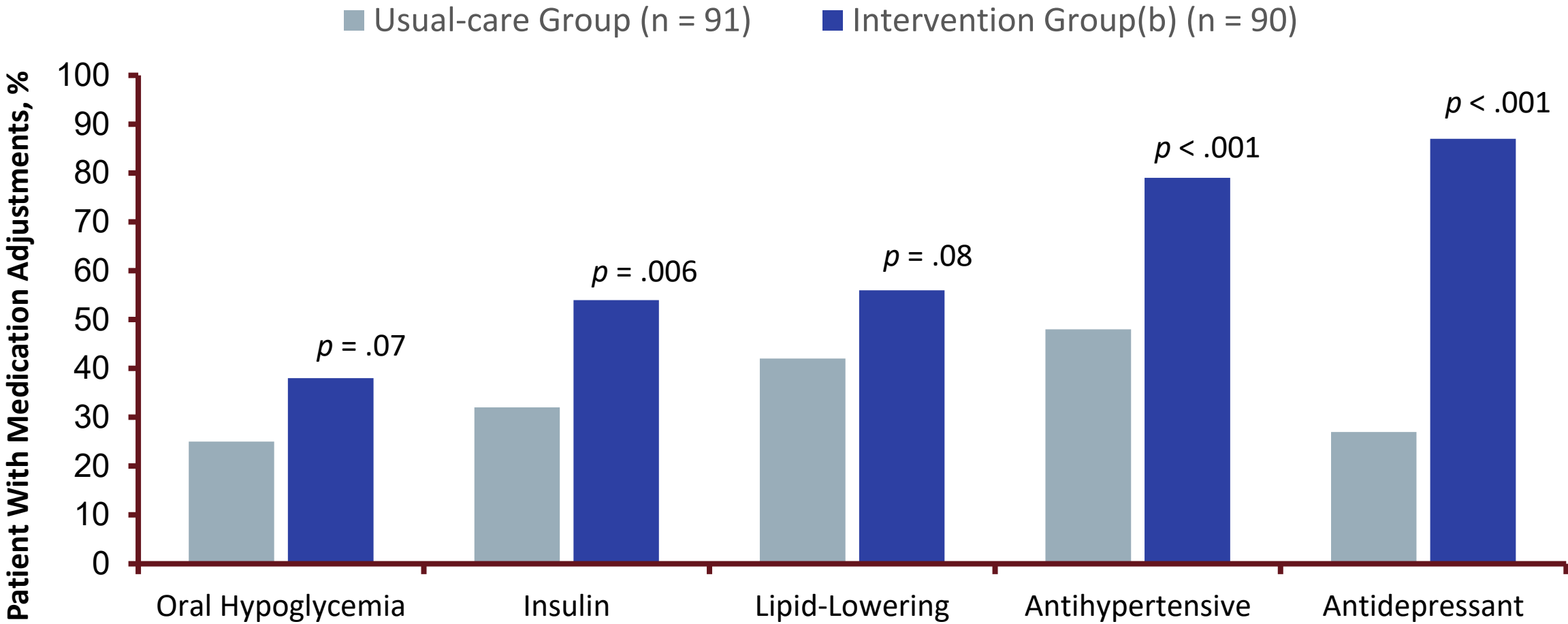
## PATIENT HEALTH QUESTIONNAIRE-9 (PHQ-9)

Over the last 2 weeks, how often have you been bothered  
by any of the following problems?  
(Use "✓" to indicate your answer)

	Not at all	Several days	More than half the days	Nearly every day
1. Little interest or pleasure in doing things	0	1	2	3
2. Feeling down, depressed, or hopeless	0	1	2	3
3. Trouble falling or staying asleep, or sleeping too much	0	1	2	3
4. Feeling tired or having little energy	0	1	2	3
5. Poor appetite or overeating	0	1	2	3
6. Feeling bad about yourself — or that you are a failure or have let yourself or your family down	0	1	2	3
7. Trouble concentrating on things, such as reading the newspaper or watching television	0	1	2	3
8. Moving or speaking so slowly that other people could have noticed? Or the opposite — being so fidgety or restless that you have been moving around a lot more than usual	0	1	2	3
9. Thoughts that you would be better off dead or of hurting yourself in some way	0	1	2	3

FOR OFFICE CODING 0 + \_\_\_\_\_ + \_\_\_\_\_ + \_\_\_\_\_  
=Total Score: \_\_\_\_\_

# Measurement Based Care Mental Health vs Other Chronic Medical Conditions



Katon WJ, et al. *N Engl J Med*. 2010 Dec 30; 363(27):2611-2620.

# Practical Suggestions for Pharmacotherapy of ADHD with Comorbidities

## Substance use disorder (SUD)

### Considerations & challenges

- Risk of abuse or diversion of stimulant ADHD medication is a concern
- Treatment can reduce ADHD symptoms without exacerbating SUD

People with ADHD are **5X** more likely to develop SUD

### Prescribing recommendations

- Avoid short-acting stimulants
- Use long-acting formulations that minimize “rush and rebound”
- Some alternative formulations may be less likely to be abused: Concerta (OROS-MPH), Vyvanse (LDX, a prodrug of dexamphetamine), Cotelpla (MPH XR-ODT), ATX, VLX-XR?

## Bipolar disorder

### Considerations & challenges

- This combination of disorders worsens and complicates each

Comorbid with ADHD in **19%** of adults, also co-occurs in children

### Prescribing recommendations

- Based on recent studies in children, treat bipolar disorder and ADHD concurrently
- Monitor for any worsening of bipolar symptoms

## Anxiety

### Considerations & 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
- First-choice: MPH
- Other options: AMP, ATX, GXR (children only); VLX-XR?

## Depression

### Considerations & challenges

- Incidence increases with age

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

### Prescribing recommendations

- Severe or suicidal cases: Treating depression takes precedent over ADHD treatment
- Mild 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
- VLX-XR?; ATX is also effective for treating ADHD

GXR=guanfacine extended release; LDX=lisdexamfetamine dimesylate; AMP=amphetamine; ATX=atomoxetine; DEX=dextroamphetamine; VLX-XR=viloxazine extended release; OROS=osmotic controlled release oral delivery system; OTD=orally disintegrating tablet.

Adapted from: Mattingly G, et al. CNS Spectr. 2021;26:202-221.

# How Many Patients With ADHD Do You Have To Treat To Prevent...

## NNT With ADHD Treatment:

- **3**
  - Developing conducting disorder
  - Developing an anxiety disorder
  - Developing oppositional disorder
  - Repeating a Grade
- **4**
  - Developing major depression
  - Having a car accident
- **5**
  - Developing bipolar disorder
- **6**
  - Smoking cigarettes
- **10**
  - Developing substance use disorder

# ADHD Is A Journey That's too Important to Ignore

