

# Adult ADHD: A Primer for Primary Care Physicians

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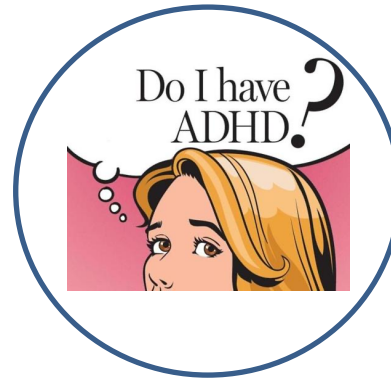
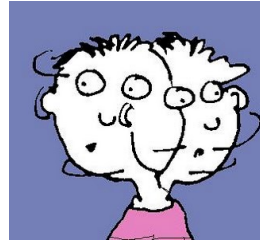
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# Disclosure: J Newcorn (Past 12 months)

Source	Consultant	Advisory Board	Speaker (Disease State)	Research Support
Adlon	X			
Corium	X	X		
Lundbeck	X			
Lumos	X			
Medice		X		
Myriad		X		
NFL	X			
NLS	X			
OnDosis	X	X		
Otsuka			X	X
Rhodes	X			
Shire/Takeda			X	X
Supernus	X			X

Additional research support provided by NIDA and NICHD

# What Is ADHD?



## Inattention

- Difficulty sustaining attention
- Trouble initiating tasks; procrastination
- Trouble completing tasks
- Loses important items
- Seems not to listen
- Cannot organize
- Easily distractible
- Forgetful
- Poor attention to detail/careless mistakes



## Hyperactivity/Impulsivity

- Intrudes/interrupts others
- “On the go”/“driven by motor”
- Runs/climbs excessively
- Cannot play/work quietly
- Squirms and fidgets
- Cannot stay seated
- Talks excessively
- Blurts out answers
- Cannot wait turn

# Adult ADHD

“ADHD is probably the most common chronic undiagnosed psychiatric disorder in adults. It is characterized by inattention and distractibility, restlessness, labile mood\*, quick temper\*, overactivity, disorganization, and impulsivity. It is always preceded by a childhood diagnosis, a disorder that is rarely inquired about and usually overlooked.”

...*Paul Wender*<sup>1</sup>

Prevalence in adults: ~4.5%<sup>2</sup>

\*Not defined as core features in DSM-5

<sup>1</sup>Wender PH. *Attention-Deficit Hyperactivity Disorder in Adults*. New York, NY: Oxford University Press; 1995.

<sup>2</sup>Kessler R et al. *Am J Psychiatry*. 2006;163:716-723.

# ADHD: DSM-5 Criteria

ADHD is classified as a neurodevelopmental disorder:

- A. Threshold level of symptoms of Inattention and/or Hyperactivity – impulsivity must be present for 6 months or more (**5 in individuals  $\geq$  17 years**)
- B. Several symptoms must be present before 12 years of age
  - **Current controversy – adult-onset ADHD?**
- C. Impairment from symptoms must be present in 2 or more settings (e.g. school, work, home, other)
- D. Significant impairment: social, academic, or occupational
- E. Symptoms must not be better accounted for by other mental (or physical) disorders

# Inattention Symptoms and their Manifestation Across the Lifespan

**Inattention-related problems and executive dysfunction represent leading reasons for seeking treatment in all age groups, and especially adolescents and adults.**

## DSM-5 Symptom Domain

- Difficulty sustaining attention
- Does not listen
- No follow-through
- Cannot organize
- Loses important items
- Easily distractible, forgetful

## Common Adult Manifestation

- Poor time management
- Difficulty
  - Initiating/completing tasks
  - Changing to another task
  - Multi-tasking
- Procrastination
- Avoids tasks that demand sustained attention
- Adaptive behavior can mitigate
  - Self select lifestyle; Support staff

# Hyperactivity Symptoms and their Manifestation Across the Lifespan

***Aimless restlessness often migrates to purposeful restlessness in adolescents and adults; and is generally less impairing with age.***

## DSM-5 Symptom Domain

- Squirms and fidgets
- Cannot stay seated
- Runs/climbs excessively
- Cannot play/work quietly
- "On the go"/  
"driven by motor"
- Talks excessively

## Common Adult Manifestation

- Adaptive behavior
  - Work long hours
  - Do many activities, multiple jobs or a very active job
- Constant activity/inability to settle down
- Avoids situations requiring low activity; easily "bored"
- Often felt rather than manifested

# Impulsivity Symptoms and their Manifestation Across the Lifespan

**Impulsivity often decreases with age, but when present, often carries serious consequences.**

## DSM-5 Symptom Domain

- Blurts out answers
- Cannot wait turn
- Intrudes/interrupts others

## Common Adult Manifestation

- Acting without thinking
- Low frustration tolerance
  - Quitting a job
  - Ending a relationship
  - Losing temper
  - Driving too fast
- Makes hasty decisions
- Impulsive aggression
  - Verbal predominates



# Persistent Symptoms of ADHD Are Associated With Potentially Serious Consequences

## Consequences of persistent inattention:

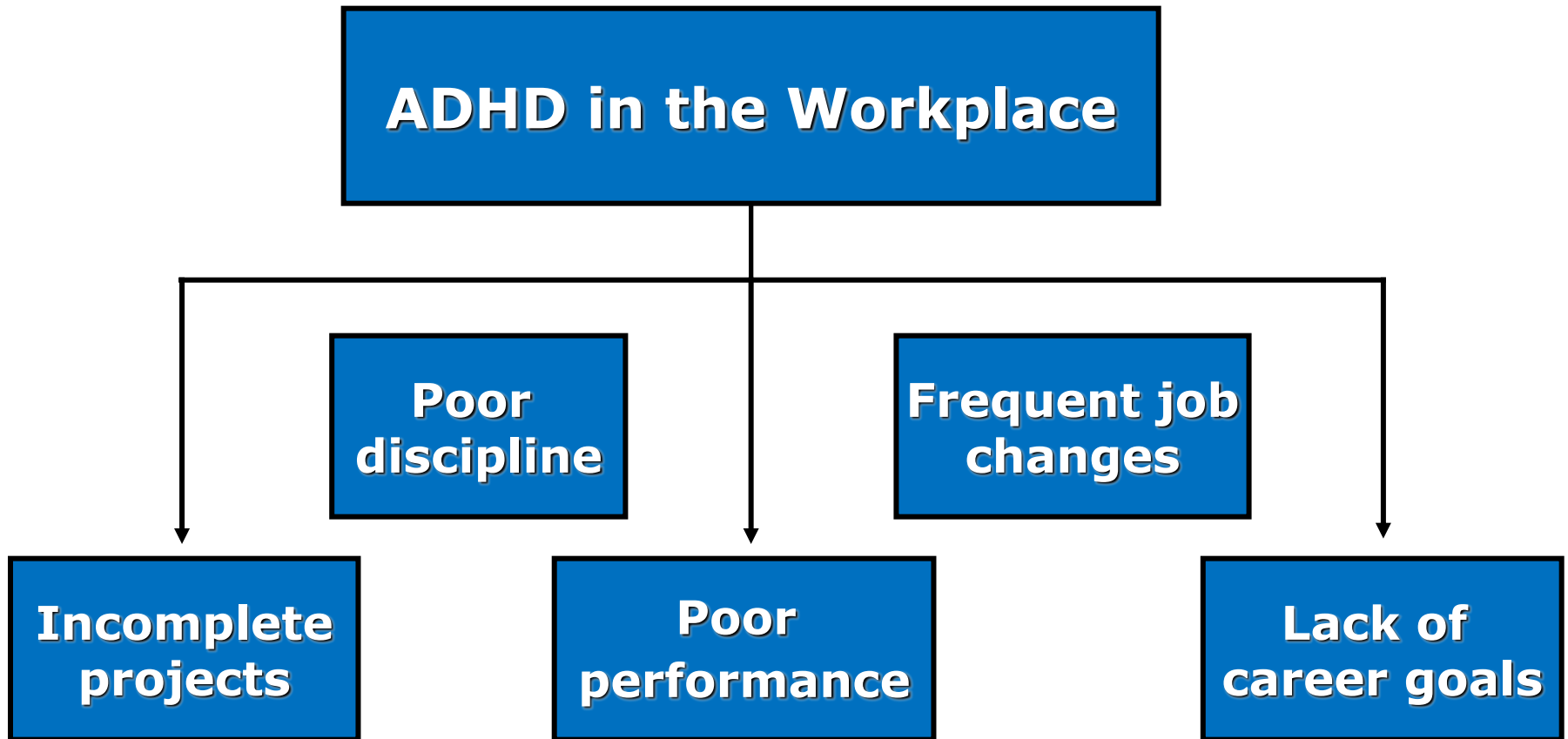
- ▶ 15–25% of children have poor academic outcome<sup>1</sup>
- ▶ Almost 30% of ADHD subjects fail grades<sup>1</sup>
- ▶ 46% of ADHD pupils suspended<sup>1</sup>
- ▶ Lower occupational attainment; lower earning across SES levels

## Consequences of persistent impulsivity:

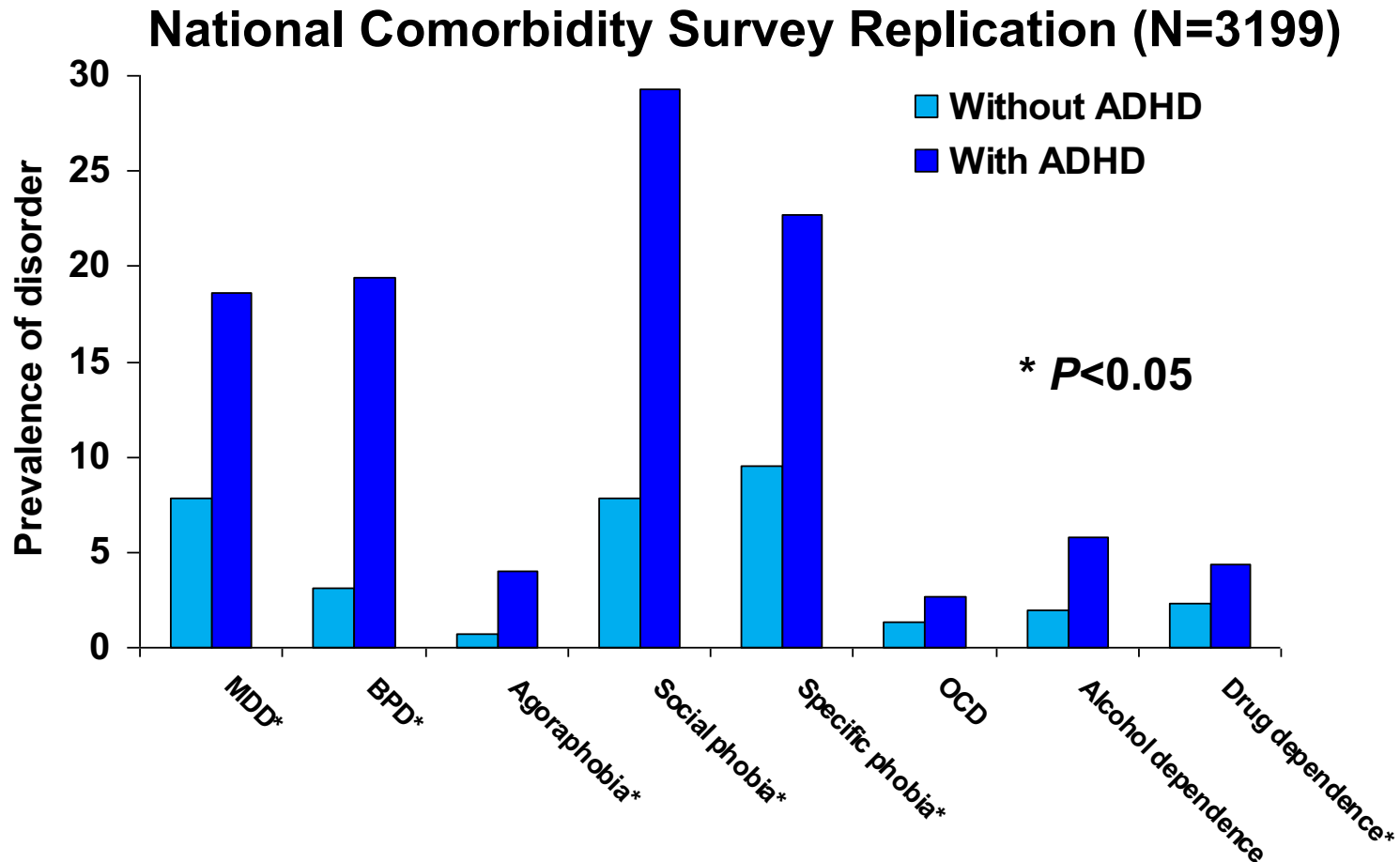
- ▶ Four times as likely to have a sexually transmitted disease<sup>2</sup>
- ▶ Three times more likely to be currently unemployed<sup>2</sup>
- ▶ Twice as likely to have been divorced<sup>3</sup>
- ▶ Twice as likely to have been arrested<sup>3</sup>
- ▶ 78% more likely to be addicted to tobacco<sup>3</sup>
- ▶ Five times more likely to have their license suspended<sup>2</sup>

1. Barkley RA. *Attention-Deficit Hyperactivity Disorder. A Handbook for Diagnosis and Treatment*, 2nd ed. New York: Guilford Press;1998. Barkley RA. *J Am Acad Child Adolesc Psychiatry*. 2006;45:192-202. 3. Biederman J et al. *J Clin Psychiatry*. 2006;67:524-540.

# Workplace Difficulties in Adults With ADHD



# Comorbidity in Adults with ADHD



Note the prominence of mood, anxiety and substance use disorders

# Summary: Clinical Presentation and Biological Basis of ADHD Across the Lifespan

- ▶ ADHD is a highly prevalent and impairing condition which persists across the lifespan
  - Impairment in many functional domains beyond school
  - Often difficult to recognize in adults
  - **Most adults are not diagnosed or treated**
- ▶ ADHD is a neurobiologically-based disorder
  - High heritability - ~75% in twin studies
  - Multiple neural networks – executive, reward, salience
- ▶ Recent models of ADHD highlight the importance of symptomatic/functional domains not described in DSM
  - Expanded view of executive dysfunction
  - Mood dysregulation
  - Important roles of motivation and salience

# Evaluation and Treatment of ADHD Across the Lifespan



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# Why Is Evaluation of Adult ADHD Complex?

- ▶ Core symptoms of ADHD are present in all individuals to some extent
  - Focus on impairment
- ▶ Comorbidity is common
  - Are symptoms from ADHD or a comorbid disorder?
  - Longitudinal history is critical
- ▶ Impairment in 2 realms of life can be relative and difficult to determine
  - Especially for the high-functioning patient
- ▶ Retrospective recall of symptoms problematic
- ▶ No litmus test to verify the diagnosis

# Why Do We Treat ADHD?

- ▶ Decrease level of core symptoms
- ▶ **Minimize impairment from core symptoms**
  - Improvement over time is likely linked to improved functional status that follows treatment of symptoms
  - Examples: academic and/or occupational problems related to attention, task completion, time management, etc.; relationship problems, self-esteem
- ▶ Alter course of other disorders?
  - Treat symptoms commonly associated with other axis I or axis II disorders, including personality disorders
  - Decrease risk for the emergence of other disorders

# ADHD Treatment Guidelines

- Guidelines: AAP 2019<sup>1</sup>; AACAP, 2007<sup>2</sup>
  - Assessment: Use established rating scales for diagnosis and monitoring treatment; assess for comorbidity
  - Treatment:
    - 4-5 years: start with evidence based behavioral Rx
      - Methylphenidate recommended if symptoms are still moderate to severe with EBT, or if EBT is not available
    - 6-18 years: preferable to use BOTH. Prescribe FDA approved medications and an EBT
      - Stimulant > Atomoxetine > Guanfacine XR > Clonidine XR
      - Target problems in multiple settings
      - Address adherence issues
    - **Adult: No US guidelines available; extrapolate from guidelines and best practices in treating adolescents**



# Environmental Modifications for Individuals with ADHD

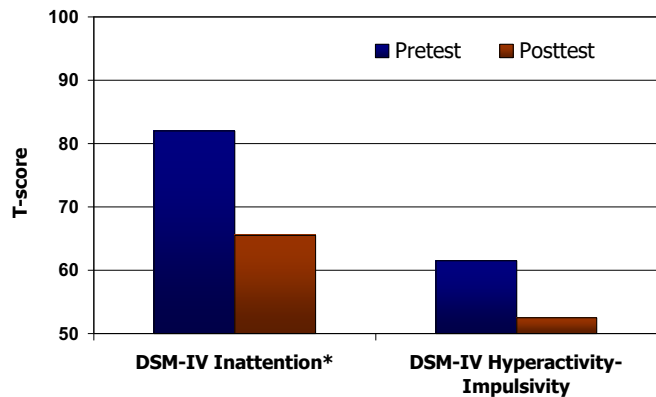
- ▶ Structure environment
  - Identify and avoid distracting environments
    - e.g., shop in smaller stores, avoid working in cubicles
  - Organize physical space (e.g., organize and label cupboards)
  - Establish centers (e.g., for bills, messages)
- ▶ Alter communication regarding tasks and establish methods for implementation
  - Examples: structure time, brief instructions, create work interests
- ▶ Use external aids:
  - Examples: electronic calendars with day planners, tape recorders, note pads, checklists, reminder alarms, and various task-specific devices (e.g., pillboxes or key finders)

# Remediation of Metacognitive Deficits in Adults with ADHD

## Targeted Domains



## Therapeutic Interventions



\*  $p < .001$



- Break down complex tasks
- Effective use of planners/organizers
- Contingent self-reinforcement
- Positive and negative visualization

# ADHD Medications Worldwide\* (approved and investigational)



## Stimulants

### Methylphenidate

Short Acting

Intermediate

Long Acting

Ritalin #  
Focalin\*

Ritalin SR #  
Metadate ER #

Concerta #  
Metadate CD #  
Ritalin LA #; Focalin XR\*  
Daytrana (patch) #  
Aptensio XR #; **Adhansia XR\***  
**Jornay PM\***, **Azstarys\***  
Quillivant (liquid) # Quillichew #; Cotempla-XR-ODT #

### Amphetamine

Short Acting

Intermediate

Long Acting

Dextrostat†  
Dexedrine tabs†

Dexedrine Spansule†  
Adderall‡  
Evekeo ‡

Adderall XR‡  
Vyvanse †  
(tablets/chewable)  
Adzenys (ODT) ‡  
Dyanavel (liquid and **tablet formulations**) ‡  
Mydayis ‡

Novel stimulant formulations (including tamper resistant)

Emerging or relatively new to market

#d,l-methylphenidate  
\*dexmethylphenidate  
†dextroamphetamine sulfate  
‡racemic amphetamine  
¶atomoxetine  
€ Viloxazine XR

§tricyclic antidepressants (many brands)  
\*\*modafinil  
††bupropion  
‡‡guanfacine  
¶¶clonidine  
§§venlafaxine

## Non-Stimulant

Approved

Not Approved

Investigational Drugs

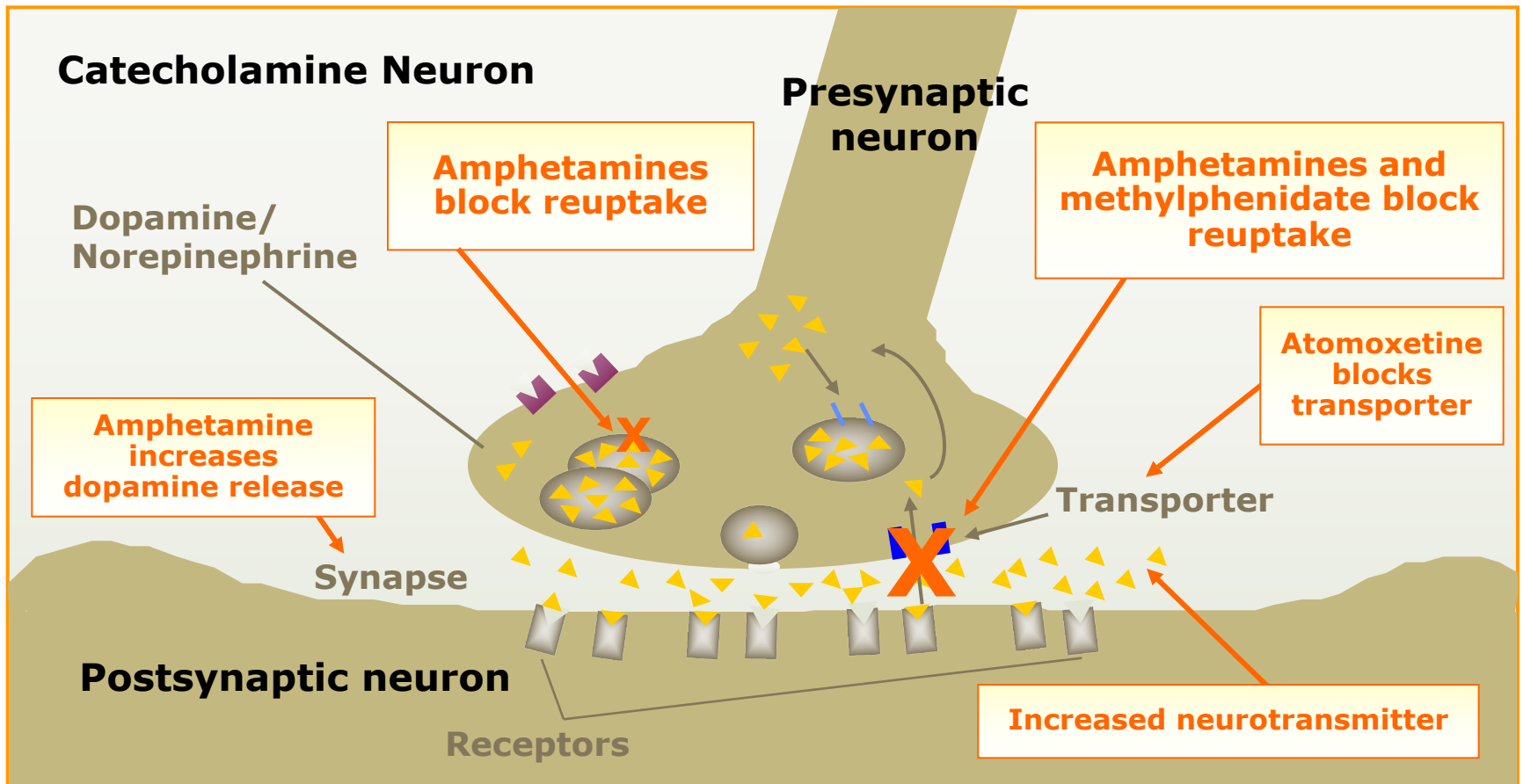
Strattera¶  
**Qelbree**€  
Intuniv ‡‡  
Kapvay¶

TCAs§  
Provigil\*\*  
Wellbutrin, Zyban††  
Tenex‡‡  
Catapres¶¶  
Effexor/Pristiq§§  
Duloxetine/Reboxetine

Centanafadine (Dasotraline)  
(Fasoracetam)  
(Mazindol)  
Misc. early phase

\*Not all drugs and/or formulations available in all countries

# Stimulants and Atomoxetine: Neurochemical Mechanisms of Action



Adapted from: Wilens TE and Spencer TJ. In: Handbook of Substance Abuse; 1998;  
Solanto MV. *Behavioral Brain Research*. 2002;130:65-67

# Benefits of Acute Stimulant Treatment

- **Core Symptoms**

- Inattention
- Impulsivity
- Hyperactivity

ES for core symptoms is  
~0.8-1.1 across studies

Time-action properties  
complicate response

- **Associated Features**

- Noncompliance
- Impulsive aggression
- Social interactions
- Academic efficiency
- Academic accuracy
- Family dynamics
- Self-esteem

ADHD Practice Parameters. *J Am Acad Child Adolesc Psychiatry*. 1997;36:85S.  
Greenhill LL, et al. *J Am Acad Child Adolesc Psychiatry*. 1999;38:503-512.

# Stimulants:

## Dosing, Titration and Efficacy

### ▶ Dose range

- Methylphenidate: 1.0 mg/kg daily
- Amphetamine: 0.5 mg/kg for DEX and MAS
- Large degree of inter- and intra-individual variability
- No comparable weight-based method for estimating dosage for MPH patch and LDX

### ▶ Titration

- Sequential dose escalation; every few days or every week; follow ADHD ratings, HR/BP
- Important to test multiple doses to find optimal response (e.g., high dose titration in MTA Study)

### ▶ Efficacy

- Effect size (ES) of 0.8-1.1 or higher, depending on study
- Slight ES favoring AMP over MPH

# Stimulants in Adolescents and Adults with ADHD: General Observations

- Treatment targets often differ in adolescents and adults
  - Predominance of inattention-related impairments
  - Treating mood dysregulation as an associated feature
- Need for treatment often extends for longer periods
- All major medication classes are now approved in adults
- Approved doses often not the same in children and adults
  - Lower approved doses of stimulants in adults is not intuitive
  - Effect sizes often larger at higher but non-approved doses, depending on the medication and the analysis
- Important to dose **adequately and treat throughout day**
  - Higher absolute but lower mg/kg dose in adolescents and adults
  - Use mg/kg calculation to estimate adequacy of dose
- Safety considerations in adults
  - Assess risk for cardiovascular AEs at baseline and sequentially after beginning treatment

# Stimulant Adverse Effects

- ▶ Common Side effects:
  - Decreased appetite, Headache, Nausea/abdominal pain, Insomnia (but also a common problem in ADHD), Palpitations, Irritability/Aggression, “Rebound” when drug wears off, Rash/anaphylaxis, Decreased growth rate, Dizziness
- ▶ Rare side effects
  - Tics - stimulant thought to unmask rather than cause disorder
  - Risk of sudden cardiac death – uncertain relationship; large-scale data base studies find not increase risk over general population rates
  - Psychiatric risk (psychosis, mania, suicidal ideation)
  - Lower seizure threshold
- ▶ Concern about Misuse/Abuse/Diversion:
  - Up to 35% of college students!
  - State registries monitor use
- ▶ *Monitor HR, BP, height, weight, signs of diversion*



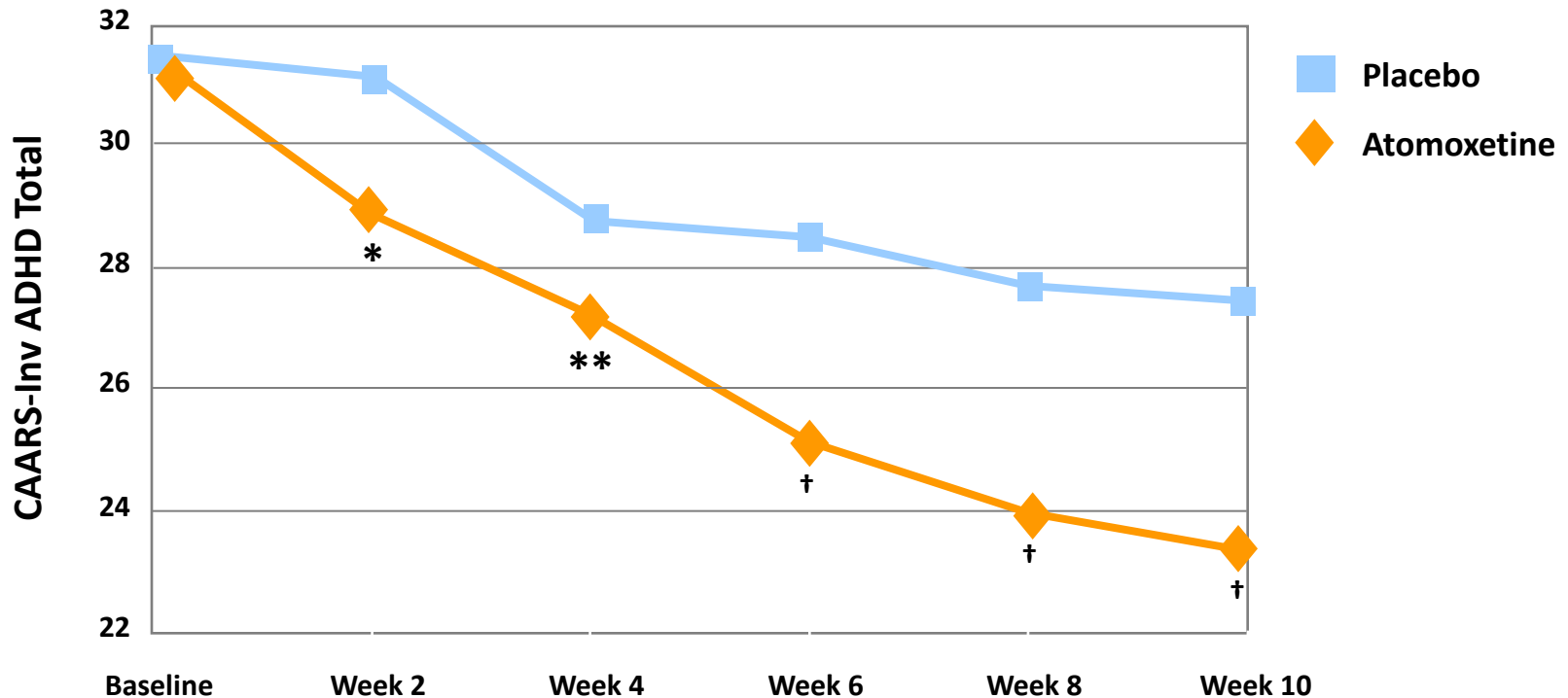
# New Findings Confirm Very Low or Absent Cardiac Risk of Stimulants

- Reviewed cardiac events in 171,126 privately insured youth ages 6 – 21<sup>a</sup>
  - Clinical diagnoses of cardiovascular events and symptoms were rare and not associated with stimulant use<sup>a</sup>
- Examined 150,359 stimulant users ages 25 – 64, compared with double the number of matched controls<sup>b</sup>
  - Current or new use of ADHD medications, compared with nonuse or remote use, was not associated with an increased risk of serious cardiovascular events<sup>b</sup>

# Rationale for Non-stimulant Treatment of ADHD

- ▶ Stimulants are extremely effective, but:
  - Poor response or tolerability in some patients
  - Sub-optimal response is not uncommon
    - Consider alternative treatments
    - Consider combination treatment
  - Relative or labeled contraindications for some comorbid conditions (e.g., tics, anxiety, substance abuse)
  - Some patients will not take stimulants
  - Risk for diversion or abuse of Schedule II drugs

# Atomoxetine in Adults with ADHD



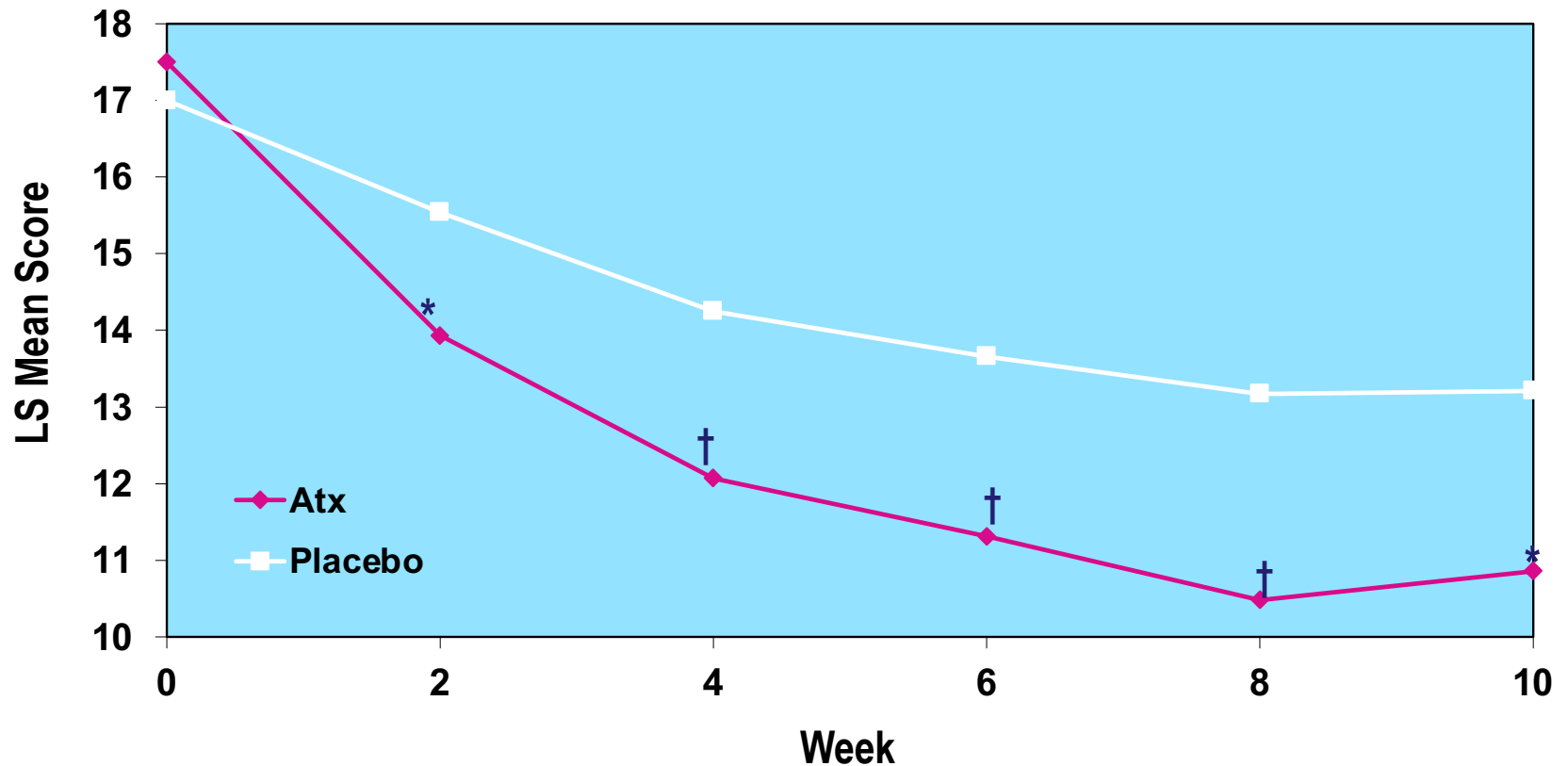
\* $P < 0.003$ ; \*\* $P < 0.05$ ; † $P \leq 0.001$ .

Ns = 280 + 256 = 536 adults

Target dosage to 120 mg/d - mean dose circa 92 mg/d

10 wk study duration

# Atomoxetine in ADHD + Anxiety Disorders: Pediatric Anxiety Rating Scale (PARS) Total Score



Strattera	N	55	55	53	49	46	45
Placebo	N	58	58	53	52	50	48

\*p<.05 †p<.01

Geller et al., *JAACAP*, 2007

# Atomoxetine: Dosing, Titration and Efficacy

## ► Dose range

- Target dose: 1.2 mg/kg
- Top labeled dose: 1.4 mg/kg
- Good safety data up to 1.8 mg/kg
- Little evidence of incremental improvement with higher doses (but tested up to 3 mg/kg)

## ► Titration

- Sequential dose escalation; every few days to every week; follow ADHD ratings, HR/BP
- Slower titration and bid dosing minimize sedation
- Poor metabolizers have much longer half-life and much higher blood levels; may be able to use lower dose
  - Co-administration with fluoxetine or paroxetine can induce poor metabolic status

## ► Efficacy

- ES ~ 0.7 across studies in youth; ~0.5 in adults

# Atomoxetine Side Effects

- ▶ Somnolence/fatigue
- ▶ Nausea/abdominal pain/vomiting (less common)
- ▶ Less common:
  - Headache
  - Dry mouth
  - Insomnia (adults)
  - Slowed growth – less than stimulants (~1/2)
  - Raynaud's phenomenon
- ▶ Rare: hepatitis (monitor for symptoms but routine labs not indicated), suicidal ideation
- ▶ **Adult males: urinary retention; sexual dysfunction**

# Situations In Which Non-Stimulants *May Be Used Preferentially*

- ▶ Poor response/tolerability with stimulants
  - Generally poor response is secondary to poor tolerability
- ▶ Presence of a co-occurring condition which can be adversely affected by stimulants, and/or better treated with non-stimulants
  - e.g., anxiety, tic, sleep, or substance use disorders, growth problems
- ▶ Patient participates in competitive athletics
- ▶ Treatment of ADHD symptoms in certain conditions other than ADHD – e.g., autism

# How and When to Combine Medication Treatments for ADHD

- ▶ Short and long-acting stimulants
  - Cover longer periods; critical periods
- ▶ Stimulants and non-stimulants
  - Augment therapeutic effects
  - Minimize adverse effects (e.g., HR/BP; insomnia)
  - Lower stimulant dose
  - Treatment of comorbidity (e.g., anxiety, tic disorders)
- ▶ Medications for treatment of other disorders
  - Comorbidity
  - Be aware of possible drug interactions



# Summary and Conclusions

- ADHD is a complex and multi-faceted neurodevelopmental disorder
  - Begins in childhood and often persists over the lifespan
  - High degree of impairment and societal cost
  - Strong neurobiological basis
- Numerous medication options show very good response
  - Stimulants generally more effective than non-stimulants
  - Non-stimulants have a major role in treatment of ADHD + comorbidity, and managing risk for SUD
  - Treatment does not “normalize” ADHD, and symptoms often persist over time despite treatment
- Combined treatment can offer benefits in selected cases
  - Stimulant and non-stimulant combinations
  - Combined medication + psychosocial treatment

# Backup Slides



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# Prevalence of ADHD Across the Lifespan

- ▶ Children
  - 8-11%, depending on age and gender<sup>1</sup>
- ▶ Adolescents
  - 75% of children with ADHD have the disorder as adolescents<sup>2</sup>
- ▶ Adults
  - National Comorbidity Survey Replication: 4.4% prevalence of ADHD among US adults<sup>3</sup>
  - Only 11% of adults with ADHD are treated<sup>3</sup>
  - Self-report measures among adults applying for a driver's license: 4.7% prevalence<sup>4</sup>
  - Adult college students: 4% met DSM-IV criteria for ADHD<sup>5</sup>

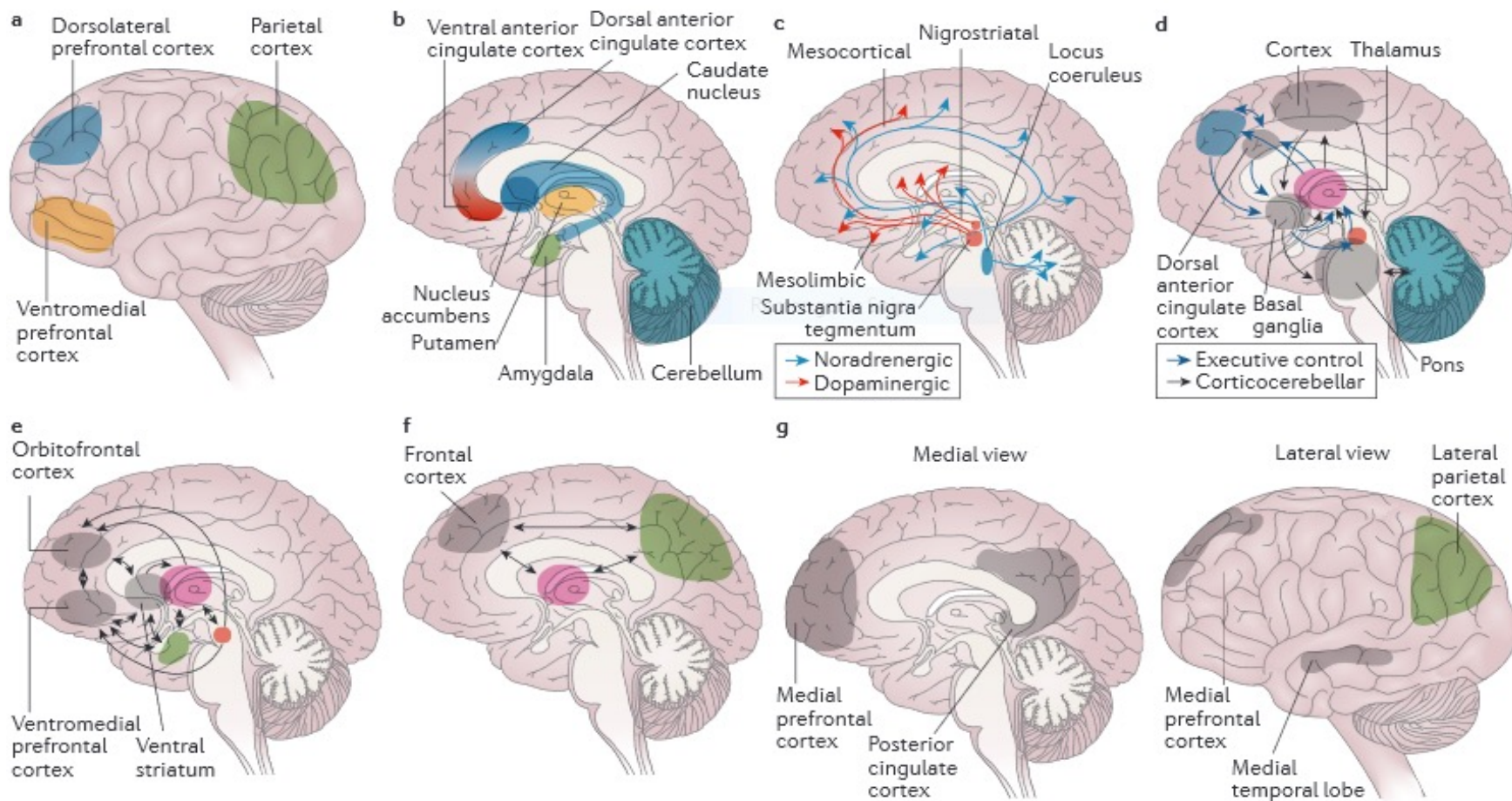
1. Visser et al., *J Am Acad Child Adolesc Psychiatry*. 2014 ; 53:34-46. 2. Wilens TE. *Psychiatr Clin North Am*. 2004;27:283-301. 3. Kessler R et al. *Am J Psychiatry*. 2006;163:716-723. 4. Barkley AR et al. *Pediatrics*. 1996;98:1089-1095. 5. Heiligenstein J et al. *Am J Coll Health*.1998; 46:185-188.

# Heritability and Genetics of ADHD

- ▶ Heritability  $\sim$  73% according to twin studies<sup>1</sup>
- ▶ No single candidate gene contributes substantially. Multiple genes contribute to the disorder<sup>2,3</sup>
  - Some candidates:
    - Dopamine: DAT1, DRD4, DRD5, DAT1/SLC6A3, DBH, DDC
    - Norepinephrine: NET1/SLC6A2, ADRA2A, ADRA2C
    - Serotonin: 5-HTT/SLC6A4, HTR1B, HTR2A, TPH2
    - Other: SNAP25, CHRNA4, NMDA, BDNF, NGF, NTF3, NTF4/5, GDNF
  - Recent GWAS data have identified 12 independent gene loci associated with the disorder<sup>4</sup>

<sup>1</sup>Nicholas & Burt, 2010; <sup>2</sup>Collingwood, 2010; <sup>3</sup>Li, 2014, <sup>4</sup>Demontis, 2019

# Current View of ADHD: Multiple Cognitive and Emotional Processes and Interacting Brain Networks



**a. Cortical brain regions; b. Subcortical brain regions; c. Catecholamine (DA + NE) mechanisms; d. Executive control networks; e. Reward network; f. Alerting network; g. Default mode network**

# Prevalence of Emotional Dysregulation (ED) In Youth and Adults with ADHD

Children: 30-40% have significant impairments

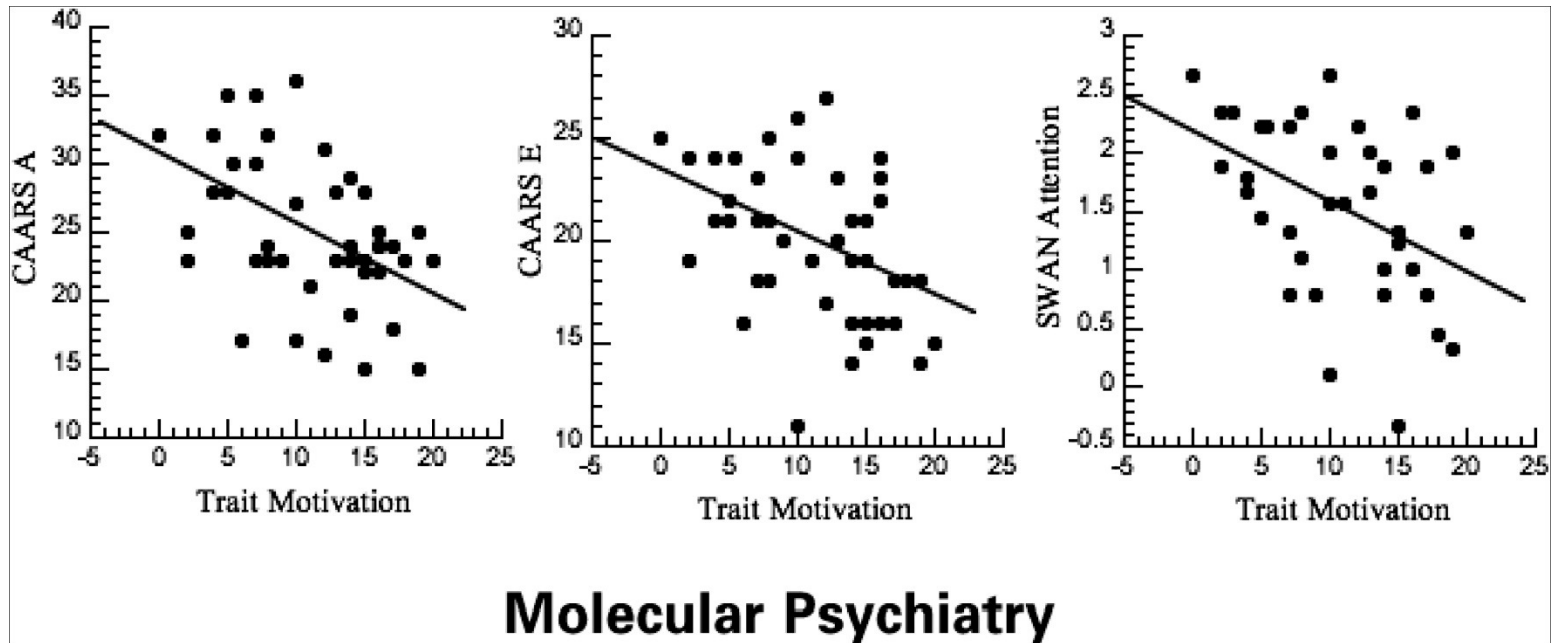
- Rage outbursts
- Irritability
- Over-reactivity
- Low frustration tolerance
- Susceptibility to anger

(Stringaris, Cohen, Pine, & Leibenluft, 2009; Barkley & Fischer, 2010; Sobanski et al., 2010; Anastopoulos et al., 2011; Spencer et al., 2011; Biederman et al., 2012; Skirrow & Asherson, 2013; Karalunas et al., 2014; Shaw, Stringaris, Nigg, & Leibenluft, 2014; Barkley, 2015; Liu et al., 2016)

Adults: over 50% report impairments

(Reimherr, Marchant, Strong, et al, 2005; Reimherr, Williams, Strong, et al, 2007; Barkley, Murphy, & Fischer, 2008; Surman, Biederman, Spencer, et al., 2011; Surman, Biederman, Spencer, Miller, McDermott, & Faraone, 2013; Barkley, 2015)

# Motivation and Inattention Symptoms Are Correlated



Ratings of motivation derived from the MPQ Schievement subscale are negatively correlated with ratings of inattention on the CAARS and SWAN scales

# Adult ADHD: Symptom Assessment Scales

Scale	Description/ Features/ Comments	Scale available from:
<b>Brown ADD Scale</b>	<b>Rates inattention/executive dysfunction; items extend beyond DSM definition of ADHD; good for high functioning adults with inattentive subtype</b>	<b><i>The Psychological Corporation</i></b>
<b>Conners Adult ADHD Rating Scale (CAARS)</b>	<b>Large item set of developmentally relevant items; DSM subscale maps onto diagnosis; self- and other-report forms</b>	<b><i>Multi Health Systems, Inc.</i></b>
<b>Wender-Reimherr Adult Attention Deficit Disorder Scale</b>	<b>Retrospective symptom scales provide age of onset data; less clearly tied to DSM-IV ADHD.</b>	<b><i>Fred W. Reimherr, MD, Department of Psychiatry, University of Utah Health Science Center, Salt Lake City, Utah</i></b>
<b>Barkley's Current Symptoms Scale</b>	<b>Dimensional scale; uses actual DSM items but not re-worked for adults; rates behavior in the past 6 months; self and other informant reports.</b>	<b><i>Barkley RA, Murphy KR. Attention-Deficit Hyperactivity Disorder: A Clinical Workbook. Second Edition.</i></b>
<b>Adult Self-Report Scale v1.1 (18-item symptom assessment and 6-item screener)</b>	<b>ADHD DSM items made developmentally relevant for adult manifestations of symptoms; rates frequency, not severity, on a 0 - 4 scale</b>	<b><i>www.med.nyu.edu/Psych/training/adhd.html and the WHO website</i></b>
<b>Adult Investigator Symptom Report Scale (AISRS)</b>	<b>Interviewer administered scale; 18 DSM-IV-TR ADHD criteria re-worked for adults; employs adult ADHD prompts to ensure adequate probing of breadth of adult symptoms.</b>	<b><i>Lenard Adler, MD, Adult ADHD Program NYU School of Medicine adultADHD@med.nyu.edu</i></b>



# How To Choose Among the Various Medication Treatments for ADHD

- ▶ Results of clinical trials
  - Mechanism of action
  - Head-to-head efficacy; comparison of effect sizes
  - Efficacy in special populations – e.g., comorbidity
- ▶ Other factors that affect medication choice
  - Nature and characteristics of response
  - Duration of effects
  - Tolerability/safety
  - Patient/physician preference (e.g., stimulant vs. nonstimulant)
  - Previous treatment experience/concomitant treatments
- ▶ **Corollary: The treatment selected may not be the one with the largest ES in clinical trials**

# Titration to “Optimal” Response

- ▶ Systematic assessment of ADHD symptoms and functional status
  - Use symptom-based rating scale
  - Identify target functional variables to be followed
  - How much improvement in symptoms translates into change in functional status?
- ▶ Systematic testing of higher doses
  - Lack of efficacy often related to inadequate dosing
  - Upward dose titration often required with increasing age and size
- ▶ Use combined treatment for selected problems
- ▶ **How to determine optimal response?**
  - 40-50% improvement in symptom score
  - CGI-S of 1 or 2 (more stringent than CGI-I)
  - End of treatment ADHD-RS score  $\leq 18$