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#### Abuse and Misuse of Stimulants for ADHD

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# Abuse and Misuse of Stimulants for Attention Deficit Hyperactivity Disorder

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### Disclosures

The author of this presentation has no relevant financial or non-financial relationships in the products described and reviewed in this presentation.



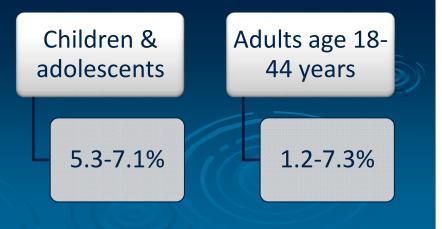
### Objectives

- 1. Compare & contrast the clinical manifestations and criteria for diagnosis of ADHD in adults & children.
- 2. Review treatment options for adults with ADHD.
- 3. Differentiate between abuse & misuse of medications.
- 4. Identify risk factors which may predispose adults to abuse & dependence to stimulant therapy for ADHD.
- 5. Discuss strategies for preventing misuse & abuse of stimulants.



### **ADHD** Overview

- Most common neurodevelopmental disorder seen in children & adolescents
- Often persists into adulthood (~50%)
  - Among these → 90% are underdiagnosed & undertreated
- Associated with social, academic & economic limitations
- ➤ risk for SUD in adolescents & adults with ADHD
- Estimated worldwide prevalence:



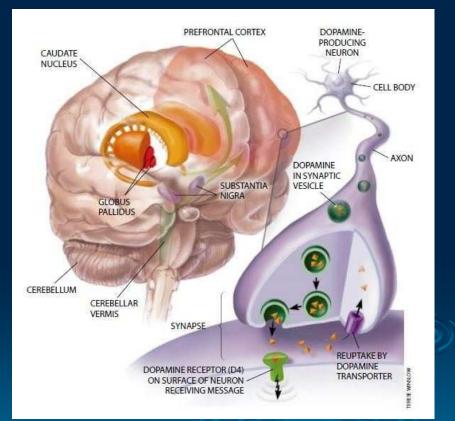
Jain R, et al. *Prim Care Companion CNS Disord*. 2017;19(5) Martinez-raga J, et al. *Ther Adv Drug Saf*. 2017;8(3):87-99. Kollins SH. *Curr Med Res Opin*. 2008;24(5):1345-1357 Epidemiology. ADHD Institute. Accessed December 12, 2018.

**ADHD**: Attention deficit hyperactivity disorder **SUD**: Substance use disorder

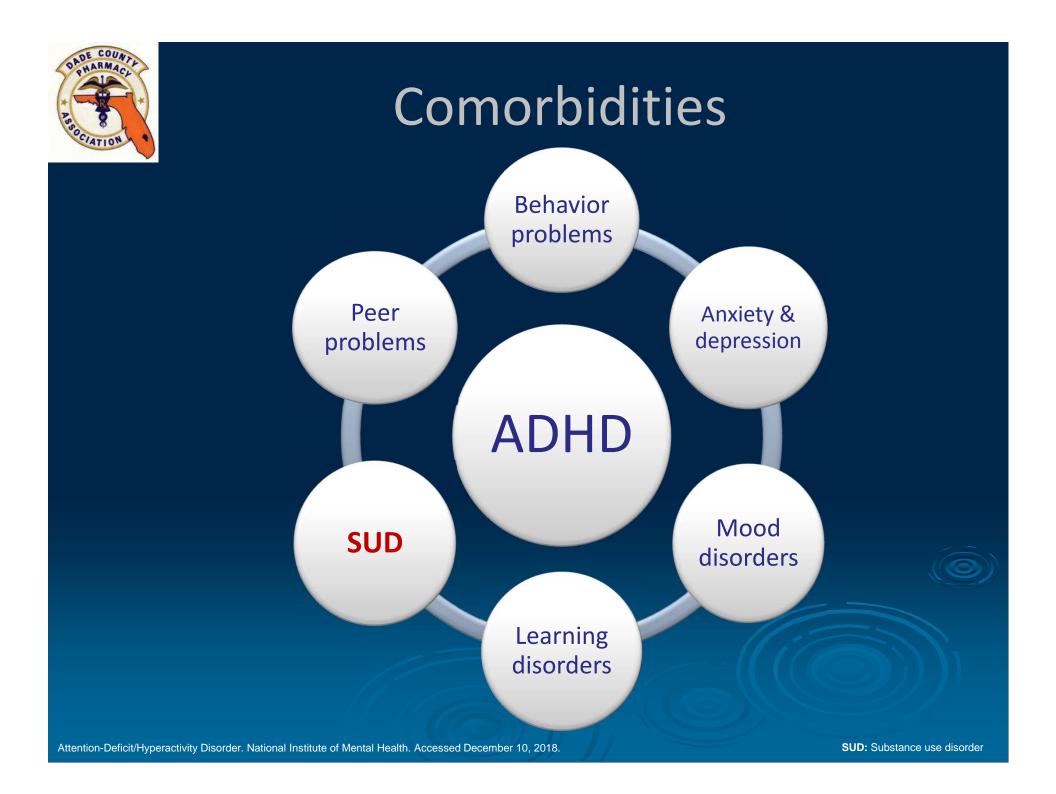


## Pathophysiology

- Exact pathogenesis unknown
- Complex, multifactorial disorder
- Disrupted DA & NE
  neurotransmission appears to
  play an important role



<u>image</u>





### **Clinical Manifestations**



### Impulsiveness

#### Hyperactivity

More prominent in adults



Jain R, et al. *Prim Care Companion CNS Disord*. 2017;19(5) Kollins SH. *Curr Med Res Opin*. 2008;24(5):1345-1357



## **Differential Diagnoses**

#### **Medical Conditions**

• Hearing impairment, thyroid disease, lead toxicity, hepatic disease, sleep apnea & drug interactions

#### **Psychiatric Conditions**

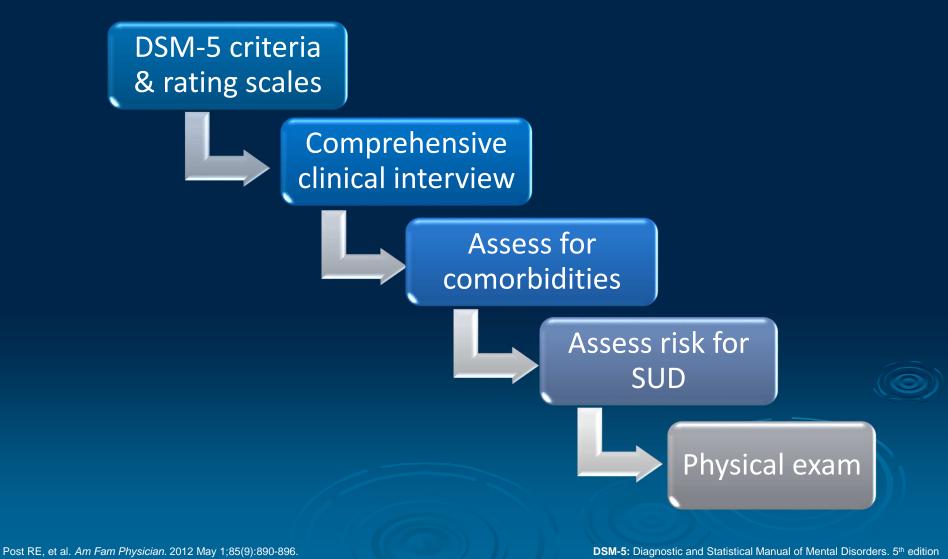
 Anxiety, depression, mood disorders, obsessive-compulsive, SUD, bipolar disorder, antisocial personality & learning disorders

#### **Medications**

• Anticonvulsants, antihistamines, caffeine, nicotine & steroids



### **Diagnostic Approach**



Attention-Deficit/Hyperactivity Disorder. National Institute of Mental Health. Accessed December 10, 2018.

SUD: Substance use disorder



### DSM-5

#### Symptoms divided into 2 domains:

- Inattention •
- Hyperactivity/Impulsivity

#### Diagnosis requires:

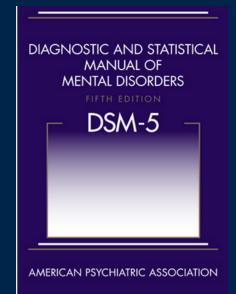
- $\geq$  6 symptoms for children ages  $\leq$  16 or
- $\geq$  5 symptoms for ages  $\geq$  17
- Symptoms present for  $\geq$  6 months & inappropriate for developmental level

#### Additional criteria:

- Several symptoms present before **age 12** & in  $\geq$  2 settings
- Evidence that symptoms interfere with social, academic or occupational functioning
- Symptoms not caused by other psychiatric disorder









### **DSM-5: Inattention**





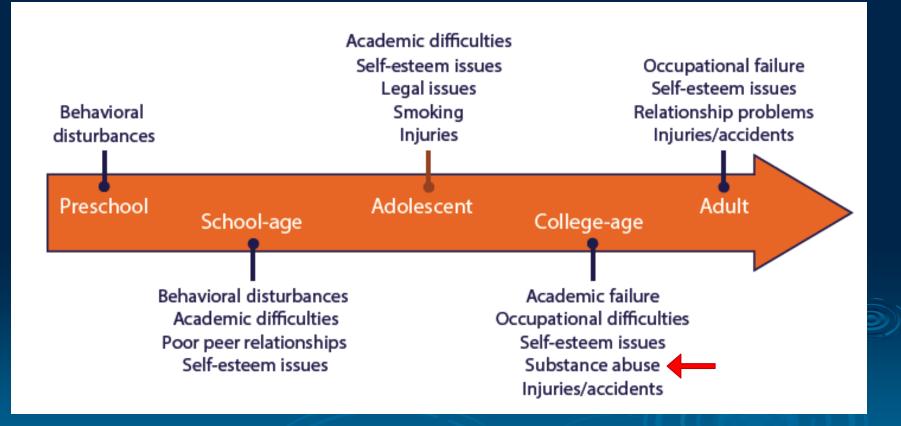
### DSM-5: Hyperactivity/Impulsivity



American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. Fifth Edition. 2013



## Timeline: Functional Impairment





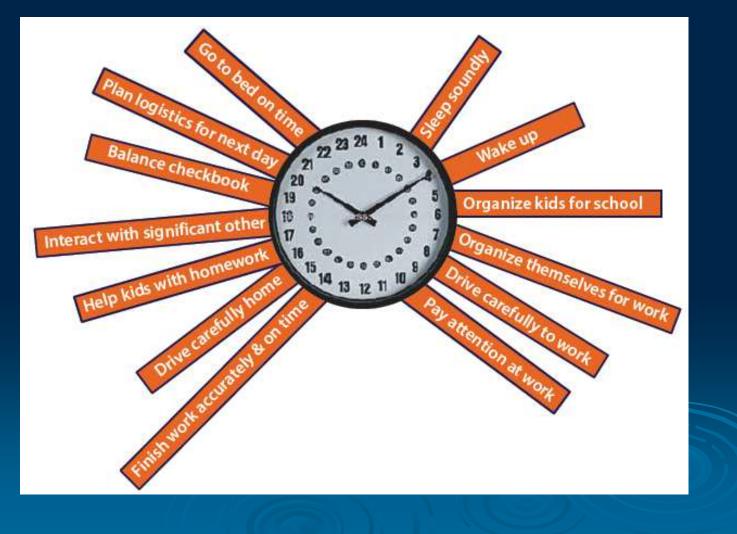
## **Overall Impact: ADHD**

- Poor academic performance
- Problems at work
- ➤ ↑ rates of unemployment
- Difficult or failed relationships
- Dangerous driving & motor vehicle accidents
- Delinquent behavior
- Impulsive sexuality
- Self-esteem issues





### Daily Challenges: Adult ADHD

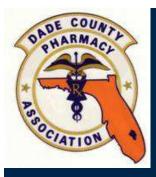




### **Consequences of Untreated ADHD**

- Major depression & anxiety
- Bipolar disorder
- SUD
- Conduct disorder
- Oppositional-defiant disorder
- Antisocial personality
- Suicide

#### Early treatment may ↓ negative outcomes



# Treatment Options for Adults with ADHD



### **Treatment Overview**

#### Assessment & diagnosis

Identify patient & family needs

Establish treatment goals

Initiate treatment

Treatment re-evaluation & monitoring



### Non-pharmacologic Treatment



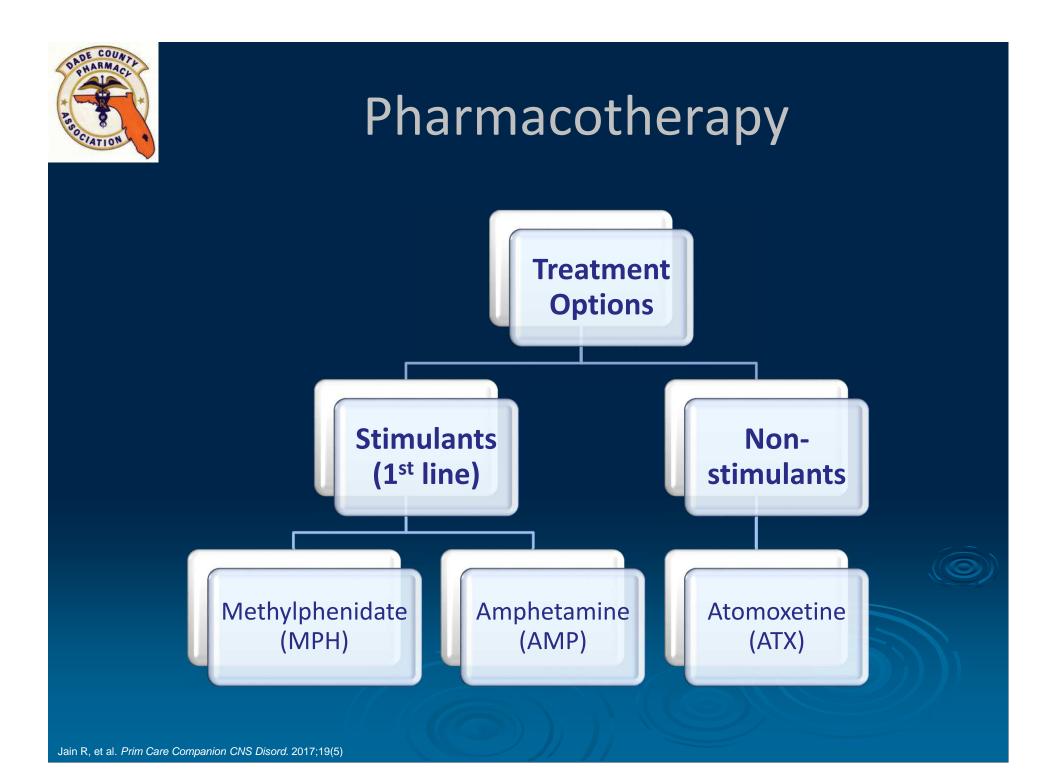
#### Options:

- Behavioral therapies (CBT)
- Psychoeducation
- Lifestyle & diet
- Helpful as *adjunct* to medication
- Behavioral therapies may be better options for patients with comorbid ADHD & SUD
  - May  $\downarrow$  risk for misuse, abuse & diversion

Future studies assessing multimodal treatment strategies are needed

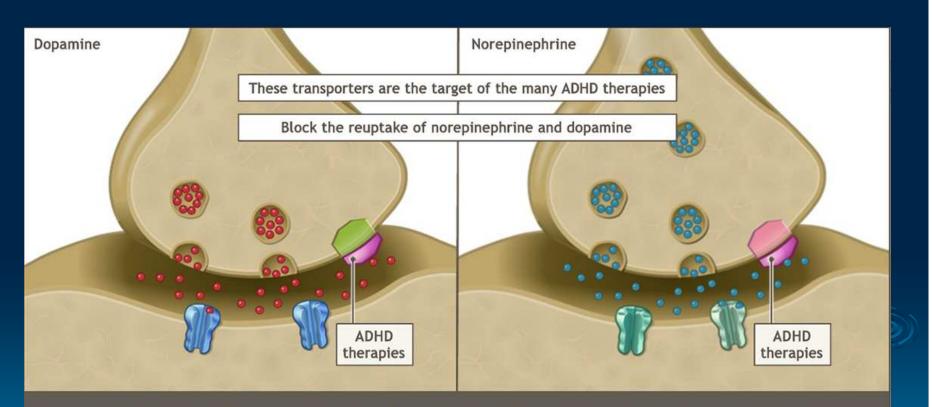
Chang Z, et al. *J Child Psychol Psychiatry*. 2014;55(8):878-85. Prescription Stimulants. National Institute on Drug Abuse. Accessed December 30, 2018. Wilens TE, et al. *Neuropsychiatry* (London). 2012;2(4):301-312.

CBT: Cognitive behavioral therapy SUD: Substance use disorder ir





### Stimulants: MOA



These transporters are the target of the many ADHD therapies that block the reuptake of norepinephrine and dopamine.



### Stimulants: Overview

- Safe & effective when used as prescribed
  - Appropriate use = *lower* risk for misuse of alcohol & other illicit drugs
- > Rapid onset of action ( $\leq 1$  hr)
- Classified as schedule II by the FDA
  - High potential for abuse, which may lead to physiological and/or psychological dependence
- Black Boxed Warning:
  - Abuse & dependence (all stimulants)

AMPHETAMINES HAVE A HIGH POTENTIAL FOR ABUSE. ADMINISTRATION OF AMPHETAMINES FOR PROLONGED PERIODS OF TIME MAY LEAD TO DRUG DEPENDENCE AND MUST BE AVOIDED. PARTICULAR ATTENTION SHOULD BE PAID TO THE POSSIBILITY OF SUBJECTS OBTAINING AMPHETAMINES FOR NONTHERAPEUTIC USE OR DISTRIBUTION TO OTHERS, AND THE DRUGS SHOULD BE PRESCRIBED OR DISPENSED SPARINGLY.

MISUSE OF AMPHETAMINE MAY CAUSE SUDDEN DEATH AND SERIOUS CARDIOVASCULAR ADVERSE EVENTS.



## Stimulants: Amphetamines

Medication	Dosage Form	Duration of Action	
MIXED AMPHETAMINE SALTS (MAS)			
[Dextroamphetamine & amphetamine]			
Adderall®	Tablet	4-6 hrs	
Adderall XR <sup>®</sup>	Capsule	8-12 hrs	
Mydayis®	Capsule	≤ 16 hrs	
AMPHETAMINE SULFATE			
Evekeo®	Tablet	4-6 hrs	
Dyanavel XR <sup>®</sup>	Oral suspension	8-12 hrs	
Adzenys XR <sup>®</sup>	ODT	10-12 hrs	
Adzenys ER®	Oral suspension	10-12 hrs	
LISDEXAMFETAMINE (LDX)*			
Vyvanse®	Capsule, chewable tablet	8-14 hrs	
*Pro-stimulant: Prodrug of dextroamphetamine			







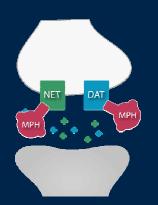
#### Recent meta-analysis concluded AMP moderately more efficacious than MPH in reducing core ADHD symptoms

Cortese S, et al. *Lancet Psychiatry* 2018; 5:727. Lexi-Drugs. Lexicomp. Wolters Kluwer Clinical Drug Information, Inc. Hudson, OH. Accessed on December 20, 2018. **ODT**: Orally disintegrating tablet **AMP**: Amphetamine **MPH**: Methylphenidate image

<u>image</u>



## Stimulants: Methylphenidate



Medication	Dosage Form	<b>Duration of Action</b>	
METHYLPHENIDATE			
SHORT-ACTING			
Ritalin®	Tablet	3-5 hrs	
Methylin®	Oral Solution	3-5 hrs	
INTERMEDIATE-ACTING			
Ritalin SR <sup>®</sup>	ODT	4-8 hrs	
Metadate ER®	Tablet	6-8 hrs	
Methylin ER <sup>®</sup>	Tablet	6-8 hrs	
LONG-ACTING			
Cotempla XR®	ODT	8-12 hrs	
Ritalin LA®	Capsule	8-12 hrs	
Concerta®	Tablet	8-12 hrs	
Aptensio XR <sup>®</sup>	Capsule	10-12 hrs	
Quillivant XR <sup>®</sup>	Oral suspension	10-12 hrs	
Daytrana®	Transdermal patch	10-12 hrs	
Quillichew ER <sup>®</sup>	Chewable tablet	12 hrs	
Jornay PM <sup>®</sup>	Capsule	12-14 hrs	
DEXMETHYLPHENIDATE			
SHORT-ACTING			
Focalin®	Tablet	3-6 hrs	
LONG-ACTING			
Focalin XR <sup>®</sup>	Capsule	8-12 hrs	





image

image image

Lexi-Drugs. Lexicomp. Wolters Kluwer Clinical Drug Information, Inc. Hudson, OH. Accessed on December 20, 2018.

## Stimulants: Adverse Effects & Monitoring

#### **Common Adverse Effects:** (dose-dependent)

 ↓ appetite, weight loss, headache, insomnia, abdominal pain, nausea/vomiting, dizziness, nervousness, emotional lability

#### **Monitoring Parameters:**

- **Prior to initiation**: Assess history and/or risk of abuse, cardiac history, consider obtaining ECG
- After initiation: Signs of misuse and/or abuse, BP, HR, chest pain, unexplained syncope, behavioral changes

Weyandt LL, et al. *Psychol Res Behav Manag.* 2014;7:223-49. Lexi-Drugs. Lexicomp. Wolters Kluwer Clinical Drug Information, Inc. Hudson, OH. Accessed on December 20, 2018.



## Stimulants: Benefits & Downfalls

#### **Benefits** (when used appropriately)

- Improve *sustained, focused* attention (vigilance)
- May improve executive function
- May improve long-term retention of information
- Facilitate consolidation of information

#### Downfalls

- May worsen *selective* attention & distractibility
- Do not improve (may impair) short-term acquisition of information and/or cognitive flexibility
- Not shown to improve learning & application of knowledge



### Non-Stimulants: Overview

- Option for individuals who fail stimulant therapy or if stimulants contraindicated
- Recommended for patients with comorbid ADHD & SUD
- Less potential for abuse than stimulants
- > Variable onset of action  $\rightarrow$  2-4 weeks





## Non-Stimulants: Atomoxetine (Strattera<sup>®</sup>)

- Only FDA-approved non-stimulant for treating adult ADHD
- MOA: Selective NE Reuptake Inhibitor (SNRI)
- Little to no abuse potential
- Duration of action: 24 hrs
- Onset of action: 1-2 weeks





## Non-Stimulants: Bupropion (Wellbutrin<sup>®</sup>)

- Off-label use
- MOA: relatively weak inhibitor of NE & DA reuptake
- Option for adults with comorbid ADHD & depression
- Onset of action: 1-2 weeks
- Duration of action: 12 hrs (SR) to 24 hrs (XL)

Currently no direct comparisons of efficacy between bupropion & stimulants in adult ADHD





# Non-Stimulants: Modafinil (Provigil<sup>®</sup>)

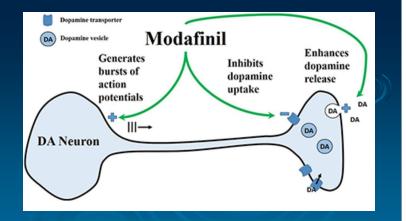


#### Off-label use

- ► MOA: Blocks DA transporters, significantly ↑ DA in the brain
  - $\downarrow$  affinity for DA receptors compared to AMP

#### Classified as Schedule IV by FDA

- Lower potential for abuse than schedule III drugs; abuse may lead to limited physical or psychological dependence relative to schedule III drugs
- Appears to improve reaction time, logical reasoning & problem-solving



imade



### Non-Stimulants: Other

#### **Alpha-2 Agonists**

- Guanfacine (Intuniv<sup>®</sup>) & Clonidine (Kapvay<sup>®</sup>)
- FDA approved for treatment of ADHD in children ages 6-17
- Efficacy, safety & tolerability in adult ADHD not well known

#### Antidepressants

- Nortriptyline (Pamelor<sup>®</sup>, Aventyl<sup>®</sup>)
- Desipramine (Norpramin<sup>®</sup>)
- Imipramine (Tofranil<sup>®</sup>)
- Venlafaxine (Effexor<sup>®</sup> & Effexor XR<sup>®</sup>)
- Shown to be less effective & more poorly tolerated than stimulants



# Misuse & Abuse of Prescription Stimulants



### **Medication Misuse**

#### **Misuse definition:**

- Using a medication with a *therapeutic* intent but taking it inappropriately
  - Use does not involve seeking psychotropic or euphoric effects
- > Examples:
  - Taking Rx medication without a Rx and/or for reasons other than prescribed, taking higher doses than prescribed, accepting or stealing Rx medication from a friend or relative
- ➤ Misuse ≈ Non-medical use
- Can *lead to* abuse & dependence



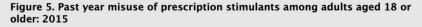
### Stimulant Misuse: Overview

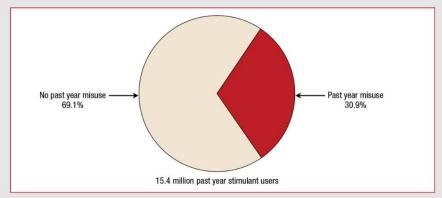
- > 2<sup>nd</sup> only to marijuana as most common form of illicit drug use
- > Prevalence  $\rightarrow$  13-23% (17% on average)
  - Greatest risk among individuals 18 -25 years of age
- ➢ Per SAMHSA → ~ 15.4 million adults reported past-year use of Rx stimulants in 2015
  - ~4.8 million (30.9%) misused Rx stimulants at least once in the past year
- Individuals both with & without ADHD misuse Rx stimulants
- > Common sources  $\rightarrow$  friends & relatives

Smith SM, et al. *Pain.* 2013;154(11):2287-96. Lakhan SE, et al. *Brain Behav.* 2012;2(5):661-77. Wilens T, et al. *J Am Acad Child and Adolesc Psychiatry.* 2006;45(2):149–157. Kroutil LA, et al. *Drug Alcohol Depend.* 2006;84(2):135-43 Weyandt LL, et al. *Exp Clin Psychopharmacol.* 2016;24(5):400-414. Lipari RN, et al. Why do adults misuse prescription drugs? National Survey on Drug Use and Health. Accessed December 21, 2018.



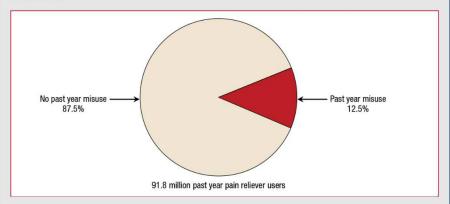
### Misuse Comparison





Source: SAMHSA, Center for Behavioral Health Statistics and Quality, National Survey on Drug Use and Health (NSDUH), 2015.

Figure 1. Past year misuse of prescription pain relievers among adults aged 18 or older: 2015

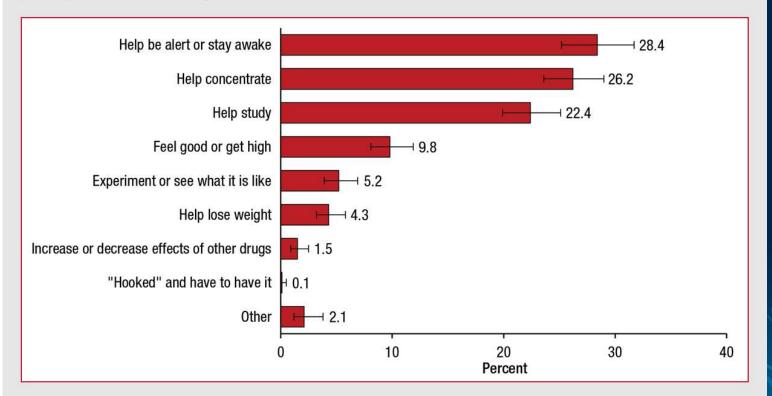


Source: SAMHSA, Center for Behavioral Health Statistics and Quality, National Survey on Drug Use and Health (NSDUH), 2015.



# Stimulant Misuse: Motives

Figure 6. Main reasons for last episode of prescription stimulant misuse among past year misusers aged 18 or older: 2015



Source: SAMHSA, Center for Behavioral Health Statistics and Quality, National Survey on Drug Use and Health (NSDUH), 2015.



# Stimulant Misuse: College Students

- Exact prevalence of ADHD among college students <u>unknown</u>
- > Rates of misuse  $\rightarrow$  8-34%
  - Estimated lifetime prevalence  $\rightarrow$  5.3-55%
- - Highest rates among fraternity members (55%)
- Risk factors:
  - Male, Caucasian, member of fraternity/sorority, low GPA, illicit drug use
- Found to be *negatively* associated with academic performance (i.e. poorer study skills, skipping class, procrastination, lower GPA)

Lakhan SE, et al. *Brain Behav.* 2012;2(5):661-77. Austic EA, Meier EA. *Drug Alcohol Depend.* 2015;152:224-9. Benson K, et al. *Clin Child Fam Psychol Rev.* 2015;18(1):50-76. Weyandt LL, et al. *Psychol Res Behav Manag.* 2014;7:223-49. Arria AM, et al. *J Drug Issues.* 2008;38(4):1045–1060



# Stimulant Misuse: Graduate Health Care Students

- Lifetime prevalence of misuse:
  - Pharmacy students  $\rightarrow$  7%
  - Graduate health care students  $\rightarrow$  11%
  - Dental & dental hygiene students  $\rightarrow$  12.4%
- > Medical students are a high risk population
  - Lifetime prevalence  $\rightarrow$  20%
  - Prevalence of use during medical school  $\rightarrow$  15%
  - Common motives → cognitive enhancement & staying awake

High prevalence among medical students may influence future prescribing patterns & physician attitudes towards patients seeking Rx stimulants

Webb JR, et al. *Ann Clinical Psychiatry*. 2013;25(1):27-32 Lakhan SE, et al. *Brain Behav*. 2012;2(5):661-77. Weyandt LL, et al. *Psychol Res Behav Manag*. 2014;7:223-49.



# Stimulant Misuse: Adults Outside University Setting

- Few studies have addressed the prevalence of Rx stimulant misuse among adults outside the university setting
- > Reported lifetime prevalence  $\rightarrow$  7.1-29%
- > 2006 2011:
  - Misuse of Rx stimulants by adults in general population  $\uparrow$  by ~67%
  - ER visits 个 by ~156%
  - Rx stimulants involved in ER visit:
    - **MAS** → 21%
    - **MPH** → 18.2%

Darredeau C, et al. *Hum Psychopharmacol.* 2007;22(8): 529–536. Weyandt LL, et al. *Psychol Res Behav Manag.* 2014;7:223-49. Chen LY, et al. J *Clin Psychiatry.* 2016;77(3):e297-304.

ER: Emergency room MAS: Mixed amphetamine salts MPH: Methylphenidate



# **Diversion of Stimulants**

### **Diversion definition**:

- The act of buying, receiving for free, trading or stealing a medication from an individual for whom it was prescribed.
- May begin in childhood, adolescence or young adulthood
- One study reported diversion in 23.3% of middle/high school students & 54% of college students



Rabiner DL. *Curr Psychiatry Rep.* 2013;15(7):375 Lakhan SE, et al. *Brain Behav.* 2012;2(5):661-77. Wilens TE, et al. *J Am Acad Child Adolesc Psychiatry.* 2008;47(1):21-31. McCabe SE, et al. *Addiction* 2005;100:96–106.



## **Medication Abuse**

### **Abuse definition:**

- Taking a medication for *non-therapeutic* purposes to obtain psychotropic or euphoric effects; often leads to addiction & dependence
  - Addiction: compulsive substance use despite personal harm or negative consequences
  - **Dependence**: associated with cravings, withdrawal symptoms and/or development of tolerance

#### **Examples**:

 Using medication to 'get high', exceeding recommended dose, continuing to take a medication after no longer needed (medically), compulsive use, not able to carry out normal daily activities

Smith SM, et al. *Pain.* 2013;154(11):2287-96. Wilens TE, et al. *J Am Acad Child Adolesc Psychiatry.* 2008;47(1):21-31 Chang Z, et al. *J Child Psychol Psychiatry.* 2014;55(8):878-85.

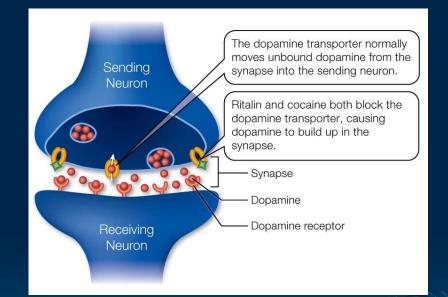


# Stimulant Abuse

#### > Approximately 80% of Rx stimulant abusers $\rightarrow$ ages 12-25 years

#### Theory behind abuse:

- Stimulants 个 DA concentrations in the brain
  - DA is involved in reinforcement of rewarding behaviors
  - Presumed to mediate abuse potential



#### Influencing factors:

 Dose, PK properties, route of administration, individual personality traits, context of use, concomitant psychiatric medications, co-morbid psychiatric disorders or concurrent illicit drug use

Martinez-raga J, et al. *Ther Adv Drug Saf.* 2017;8(3):87-99. Chang Z, et al. *J Child Psychol Psychiatry.* 2014;55(8):878-85. Kroutil LA, et al. *Drug Alcohol Depend.* 2006;84(2):135-43.

DA: Dopamine PK: Pharmacokinetic image



# **Risk Factors for SUD in ADHD**





# Does Stimulant Use Lead to SUD?

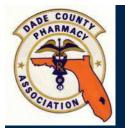
- ➤ Research shows that people of any age receiving Rx stimulants for ADHD are <u>not</u> at ↑ risk for SUD compared to the general population
- Rx stimulant use (specifically MPH) during childhood for ADHD does not appear to affect the risk of SUD in adulthood

One review showed ↓ risk of SUD by ~27%



Biederman J, et al. *Am J Psychiatry*. 2008; 165(5):597-603 Mannuzza S, et al. *Am J Psychiatry*. 2008;165(5):604-609 Kollins SH. *Curr Med Res Opin*. 2008;24(5):1345-1357 Chang Z, et al. *J Child Psychol Psychiatry*. 2014;55(8):878-85.

SUD: Substance use disorder MPH: Methylphenidate ima



# Consequences of Stimulant Misuse & Abuse

### **Adverse events:**

- > Heart failure
- » Myocardial infarction
- Stroke
- > Arrhythmias
- > Cardiomyopathy

- > Hypertension
- > Seizures
- Paranoia
- > Psychosis
- > Sudden death

#### Risk even higher when combined with other drugs or alcohol



## Stimulant Overdose

#### Signs & symptoms :

 Hyperthermia, agitation, tachycardia, hyperhidrosis, tachypnea, 个 BP, palpitations, chest pain, mydriasis, restlessness, convulsions, seizures, psychosis, nausea, vomiting, abdominal pain

#### Complications:

• Rhabdomyolysis, liver/kidney damage, cognitive deficit, death (rare)

#### Inpatient Management:

- Mainly supportive care measures
- Activated charcoal or gastric lavage
- Benzodiazepines → for sedation or persistent seizures
- Antipsychotics  $\rightarrow$  for agitation & psychosis
- Temperature control  $\rightarrow$  within 15-20 minutes



# Preventing Misuse & Abuse: Role of Prescribers

### Prescribing physicians (major source for misuse & abuse)

- Estimated 20% of individuals misusing Rx stimulants obtain them by fraudulently misrepresenting symptoms of ADHD to physicians
- Proper diagnosis & treatment of ADHD
  - Consider comorbidities & baseline risk for SUD
- $\succ$  Prescribe medications with  $\downarrow$  potential for misuse & abuse
  - Pro-stimulant, LA Rx stimulant formulations, non-stimulants
  - Avoid IR & SA formulations in patients at  $\uparrow$  risk for SUD



# Preventing Misuse & Abuse: Role of Prescribers (cont.)

- Educate patients on addictive nature of Rx stimulants
- Re-evaluate patients periodically for need to continue Rx stimulant treatment
  - Consider drug-free periods
- Regularly monitor adult use of Rx stimulants for ADHD
  - Check PDMP

#### Weyandt LL, et al. *Psychol Res Behav Manag.* 2014;7:223-49. Novak SP, et al. *Subst Abuse Treat Prev Policy.* 2007;2:32 Modesto-lowe V, et al. *Cleve Clin J Med.* 2015;82(8):506-12.

#### Interventions to minimize drug misuse based on patient risk stratification

#### If at low risk for misuse

Education, including: Abuse potential Consequences of sharing or selling Interactions with illicit substances Safe storage

Check a prescription monitoring program, if available

#### If at high risk for misuse

Education

Check prescription monitoring program

Use delayed-release preparations

Prescribe small quantities at a time

If showing red-flag behavior<sup>a</sup> Education

Check prescription monitoring program

Pill counts at each visit

Urine drug screens

\*Red-flag behavior: missed appointments, early refill requests, appearing intoxicated at visit, requesting dose increase.



### **PDMPs**

- State-run programs designed to encourage safer prescribing & prevent abuse of controlled substances
- Electronic monitoring of the prescribing <u>and</u> dispensing of controlled substances
- E-FORCSE = PDMP in Florida
- > House Bill 21
  - Requires consultation of PDMP *prior to* prescribing or dispensing a controlled substance to a patient ≥ 16 years of age
  - Dispensing must be reported to database no later than close of next business day

E-FORCSE, Florida's Prescription Drug Monitoring Program. Accessed December 17, 2018 Scott J. Florida's New Law on Controlled Substance Prescribing. Accessed December 17, 2018

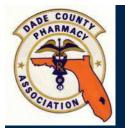




# Preventing Misuse & Abuse: Role of Pharmacists

#### Counsel patients on:

- Using Rx stimulants only as prescribed
- Health & legal risks associated with misuse & diversion of Rx stimulants (provide medication guides)
- Importance of safe storage of medication
- Dangers of co-ingestion of Rx stimulants with alcohol and/or other illicit substances
- Frequent monitoring to ensure appropriate use
  - Check PDMP
- ➤ Watch for ADHD medication shopping (i.e. overlapping prescriptions by ≥ 2 prescribers & filled at ≥ 3 pharmacies)



# Summary

- ➤ Failure to diagnose and treat ADHD in adults is linked to negative outcomes & ↑ risk for SUD
- Pro-stimulant (LDX) & LA Rx stimulant formulations less prone to misuse, abuse & diversion
- Non-stimulants are preferred options for ADHD patients at risk for SUD
- Future studies needed to assess prevalence & factors associated with adult Rx stimulant misuse outside the university setting
- > Prevention strategies are key!



# True or False?

- 1. Clinical manifestations of ADHD are the same in both adults & children.
- Behavioral therapies, such as CBT, may be effective in preventing misuse & abuse of Rx stimulant medications in patients at 个 risk for SUD
- 3. Rx stimulant medications ↑ the activity of certain neurotransmitters, such as DA & NE.





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