Stimulant Use Disorder:
Clinical Issues and Treatment Challenges

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Faculty Disclosure

- **Dr. Mooney**: Advisory Board—Alkermes; Grant/Research Support—National Institute on Drug Abuse (does not include pharmacotherapy trials for stimulant use disorder at this time).

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).
  - There are no FDA-approved treatments for cocaine and methamphetamine use disorders. The off-label use of bupropion, tricyclic antidepressants, and pemoline for the treatment of ADHD will be discussed. The off-label use of bupropion, naltrexone, modafinil, topiramate, mirtazapine, and prescription stimulants for the treatment of stimulant use disorder will be discussed.
- Applicable CME staff have no relationships to disclose relating to the subject matter of this activity.
- This activity has been independently reviewed for balance.
- Brand names are included in this presentation for participant clarification purposes only. No product promotion should be inferred.

Learning Objectives

- Describe diagnostic considerations and clinical effects of stimulant use disorder
- List 2 off-label pharmacotherapy options with preliminary evidence for the treatment of both cocaine and amphetamine use disorders
- Describe at least 2 approaches for management of ADHD in individuals with a history of stimulant use disorder

Cocaine, Methamphetamine, and Prescription Stimulants

Types of Stimulant Drugs: *Amphetamine Type Stimulants*

- Approximately 40 to 60 million users worldwide
- Amphetamine
  - Powder, tablets, liquid: Orally, injected, smoked
- Methamphetamine
  - Powder: Inhaled, smoked, injected
  - Crystal/Ice: Smoked
  - Tablets: Orally, crushed and inhaled, smoked, injected
- Major regions of use
  - Eastern and South East Asia
  - Australia and Oceania
  - North America
  - Increases in Central, Eastern, and Northern Europe
  - Increases in Middle East
  - Increases in South Africa

Types of Stimulant Drugs: *Cocaine*

- Approximately 16 to 21 million users worldwide
- Cocaine Powder: Sniffed, injected, smoked
- “Crack”: Smoked
- Major regions of use
  - South America
  - North America (predominantly major urban centers disproportionately impacts African American community)
  - Increases in Central and Western Europe
  - Increases in South and Western Africa

Methamphetamine vs Cocaine

Methamphetamine

- Synthetic
- High lasts 8 to 24 hours
- $T_{½}$: 12 hours
- Mechanism: Mainly DA release
- Medical use less common (Rx as Desoxyn®)
- Greater neurotoxicity in commonly used doses

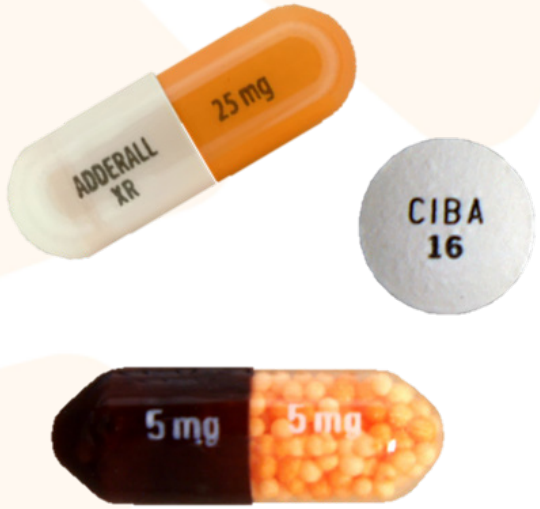
Cocaine

- Plant-derived
- High lasts 20 to 30 minutes
- $T_{½}$: 1 hour
- Mechanism: Mainly DA reuptake
- Used medically
- Not directly neurotoxic

DA = dopamine.

Types of Stimulant Drugs: *Prescription Stimulants*

- Prescription stimulants include medications such as
  - Methylphenidate (Ritalin® and Concerta®)
  - Amphetamines (Dexedrine® and Adderall®)



Stimulant Use Epidemiology

Rates of Cocaine and Methamphetamine Use

- Cocaine: 1% of the population aged ≥ 12 reported using cocaine or crack cocaine
  - 0.1% of adolescents aged 12 to 17
  - 1.9% of young adults aged 18 to 25
  - 0.7% of adults aged ≥ 26
- Methamphetamine: 0.3% of the population aged ≥ 12 reported using methamphetamine
  - 0.1% of adolescents aged 12 to 17
  - 0.4% of young adults aged 18 to 25
  - 0.3% of adults aged ≥ 26

Substance Abuse and Mental Health Services Administration. (2018). *Key substance use and mental health indicators in the United States: Results from the 2017 National Survey on Drug Use and Health* (HHS Publication No. SMA 18-5068, NSDUH Series H-53). Rockville, MD: Center for Behavioral Health Statistics and Quality, Substance Abuse and Mental Health Services Administration. www.samhsa.gov/data/sites/default/files/cbhsq-reports/NSDUHFFR2017/NSDUHFFR2017.htm. Accessed July 8, 2019.

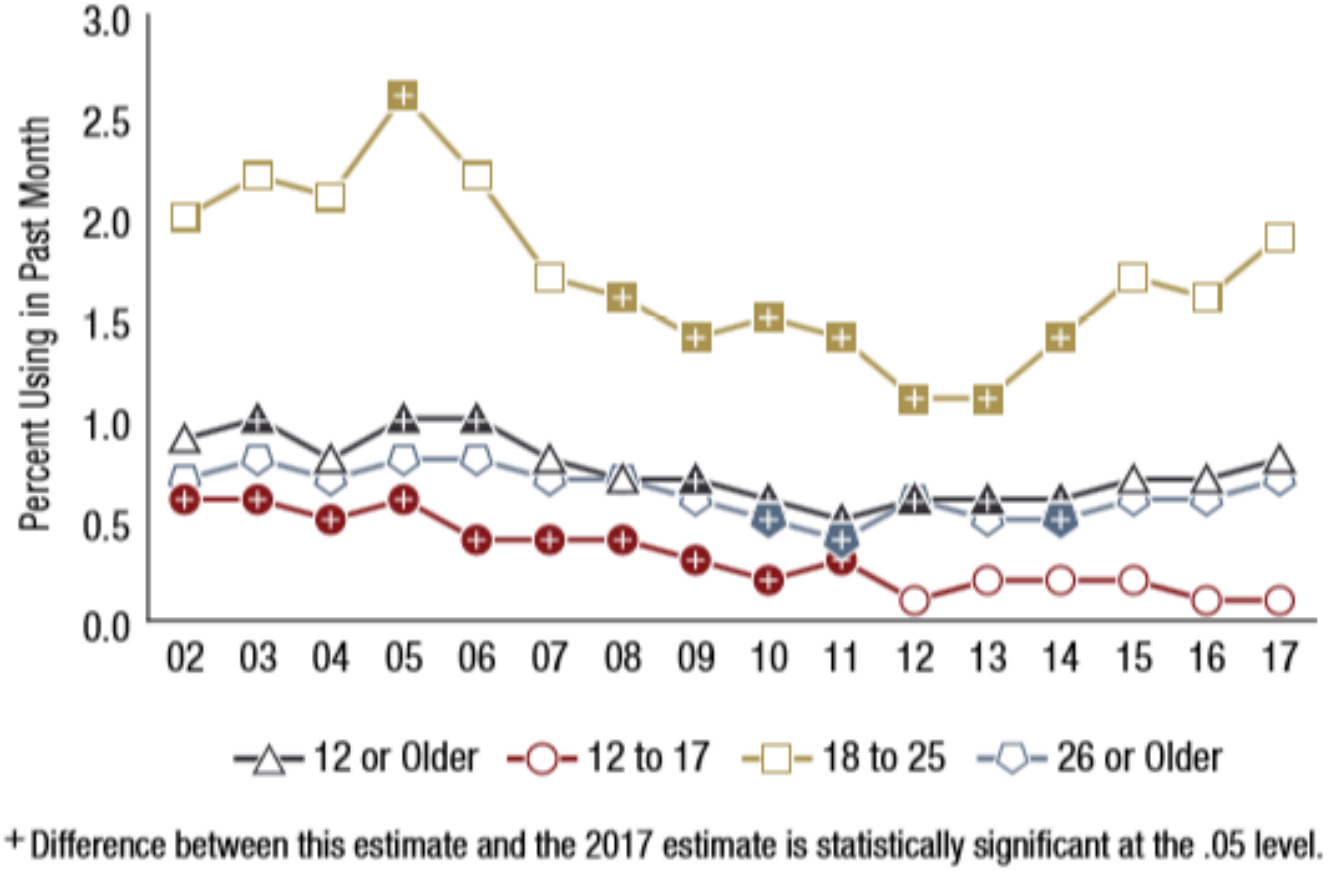
Substance Use Disorder Diagnosis in Past Year (NSDUH, 2017)

- Cocaine: Approximately 0.4% of the population aged ≥ 12 were diagnosed with CUD
  - 0.1% of adolescents aged 12 to 17
  - 0.7% of young adults aged 18 to 25
  - 0.3% of adults aged ≥ 26
- Methamphetamine: Approximately 0.4% of the population aged ≥ 12 were diagnosed with MUD
  - 0.1% of adolescents aged 12 to 17
  - 0.5% of young adults aged 18 to 25
  - 0.4% of adults aged ≥ 26

CUD = cocaine use disorder; MUD = methamphetamine use disorder; NSDUH = National Survey on Drug Use and Health.

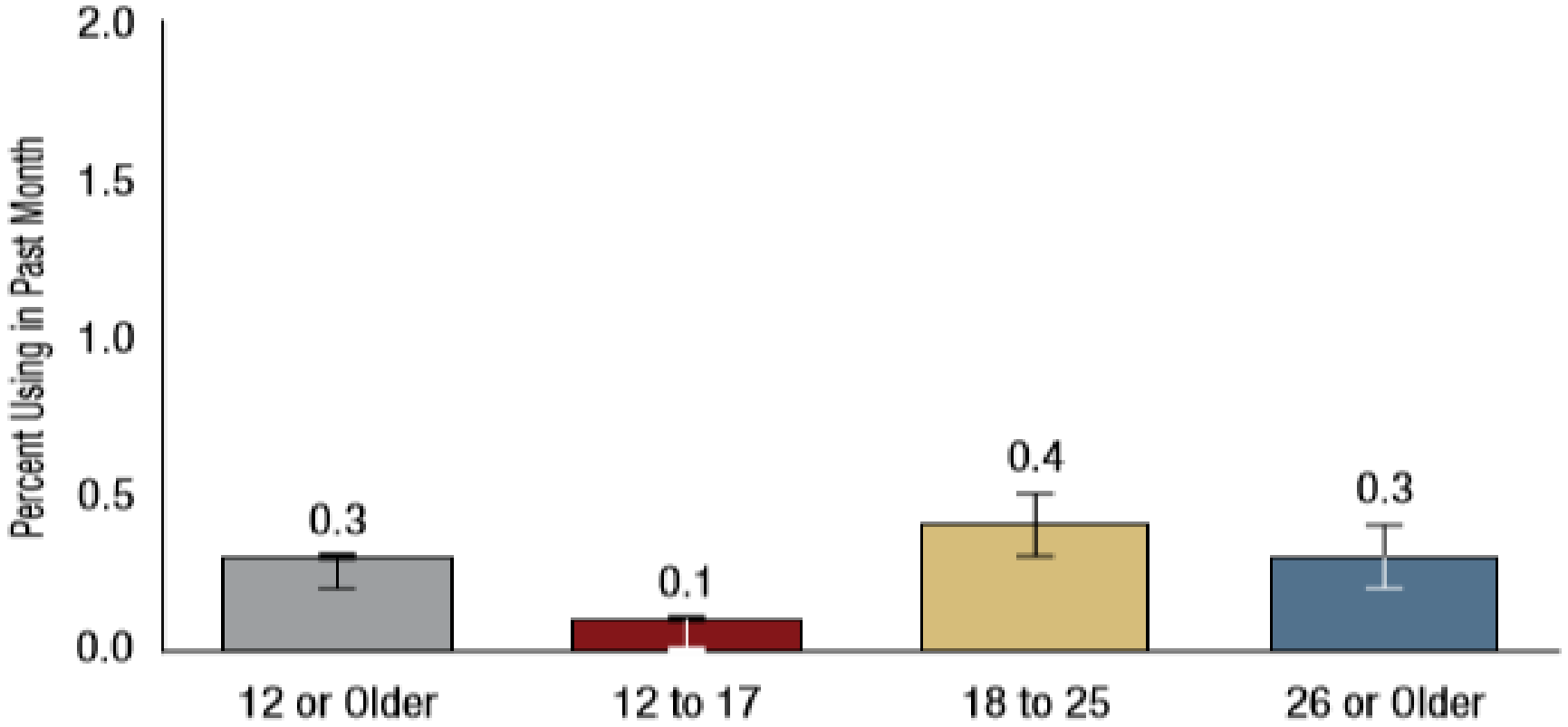
Substance Abuse and Mental Health Services Administration. (2018). *Key substance use and mental health indicators in the United States: Results from the 2017 National Survey on Drug Use and Health* (HHS Publication No. SMA 18-5068, NSDUH Series H-53). Rockville, MD: Center for Behavioral Health Statistics and Quality, Substance Abuse and Mental Health Services Administration. www.samhsa.gov/data/sites/default/files/cbhsq-reports/NSDUHFFR2017/NSDUHFFR2017.htm. Accessed July 8, 2019.

Past Month Cocaine Use by Age Group



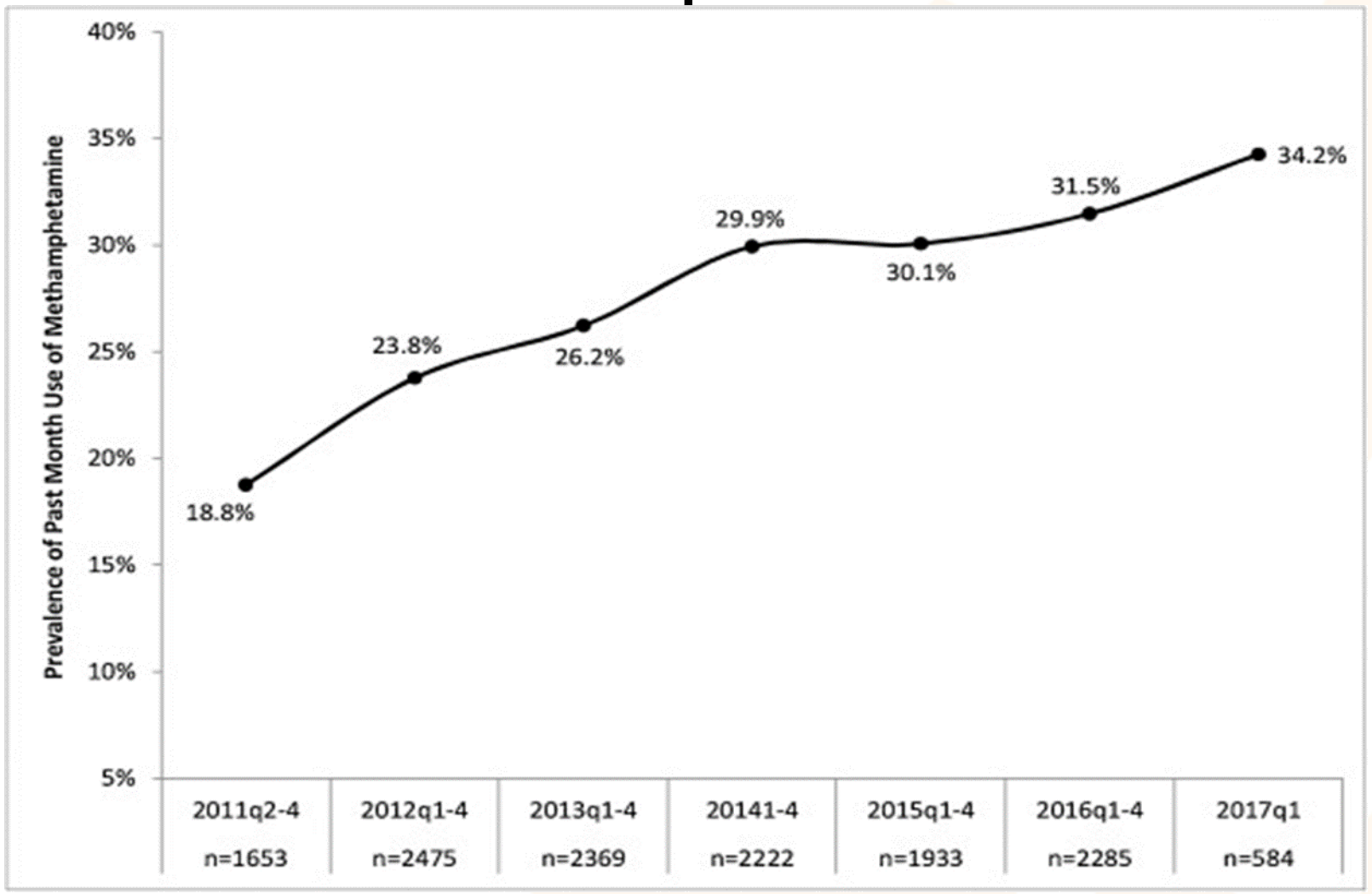
Substance Abuse and Mental Health Services Administration. (2018). *Key substance use and mental health indicators in the United States: Results from the 2017 National Survey on Drug Use and Health* (HHS Publication No. SMA 18-5068, NSDUH Series H-53). Rockville, MD: Center for Behavioral Health Statistics and Quality, Substance Abuse and Mental Health Services Administration. www.samhsa.gov/data/sites/default/files/cbhsq-reports/NSDUHFFR2017/NSDUHFFR2017.htm. Accessed July 8, 2019.

Past Month Methamphetamine Use by Age Group



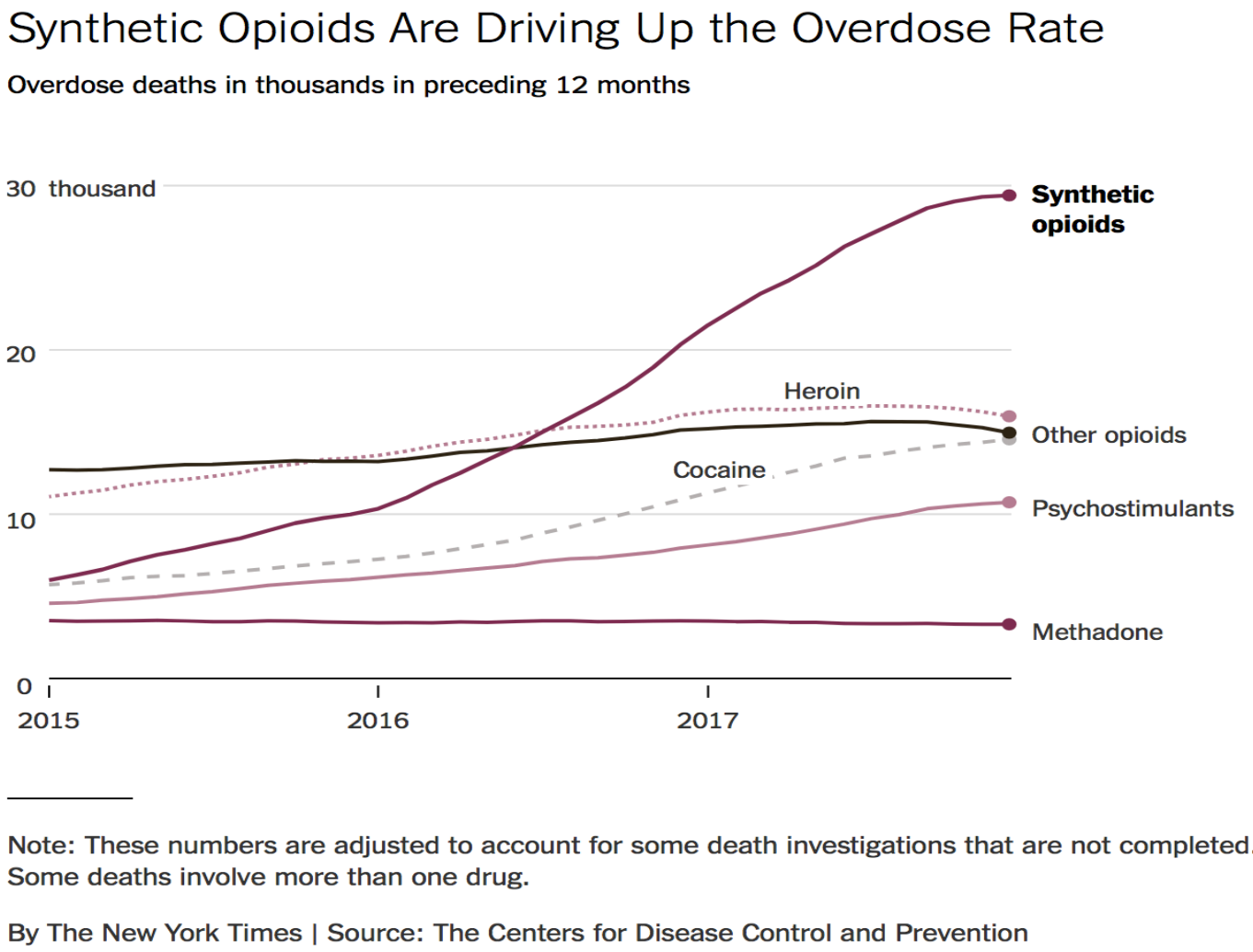
Substance Abuse and Mental Health Services Administration. (2018). *Key substance use and mental health indicators in the United States: Results from the 2017 National Survey on Drug Use and Health* (HHS Publication No. SMA 18-5068, NSDUH Series H-53). Rockville, MD: Center for Behavioral Health Statistics and Quality, Substance Abuse and Mental Health Services Administration. www.samhsa.gov/data/sites/default/files/cbhsq-reports/NSDUHFFR2017/NSDUHFFR2017.htm. Accessed July 8, 2019.

Methamphetamine Use among Patients with Chronic Opioid Use

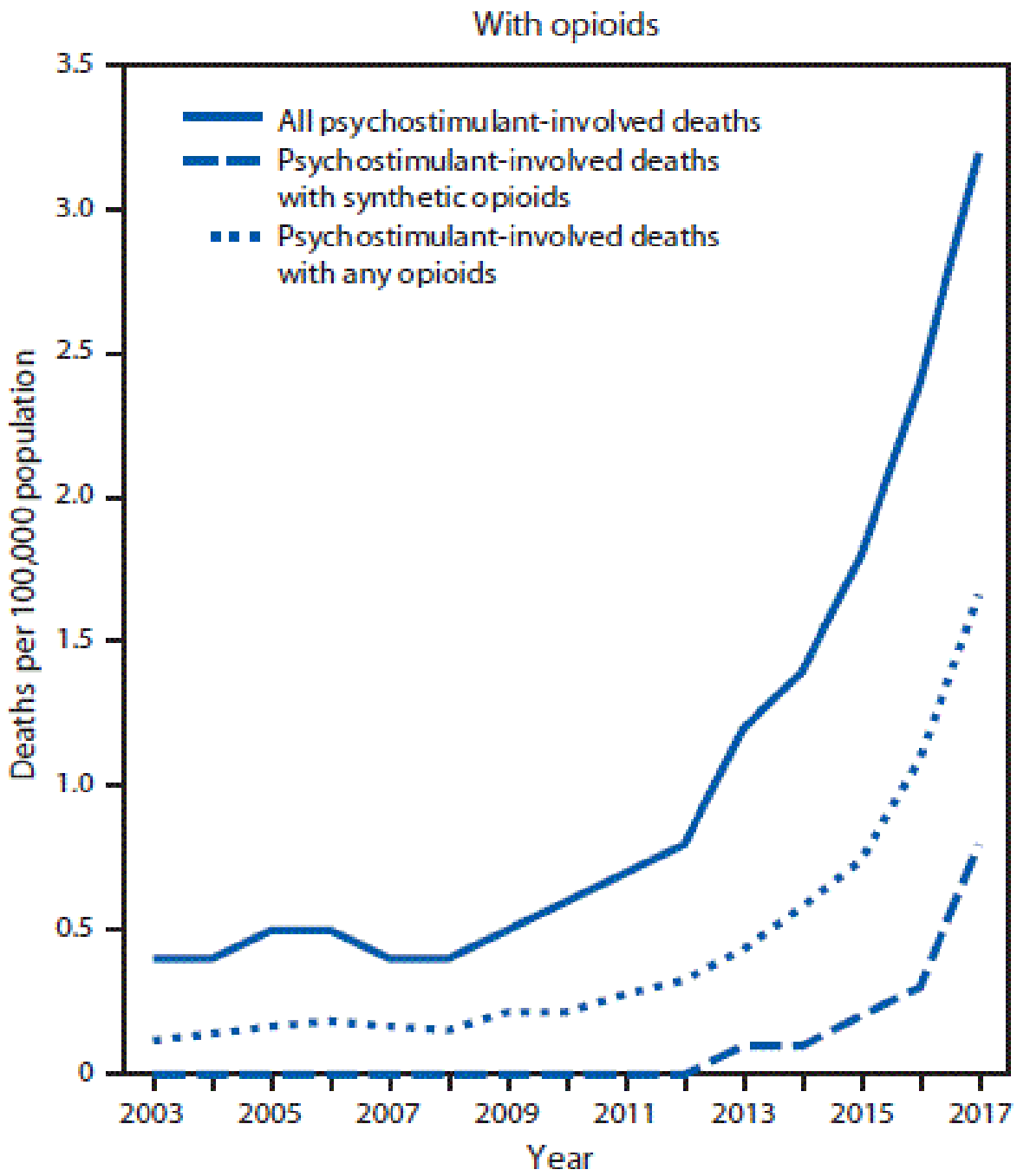


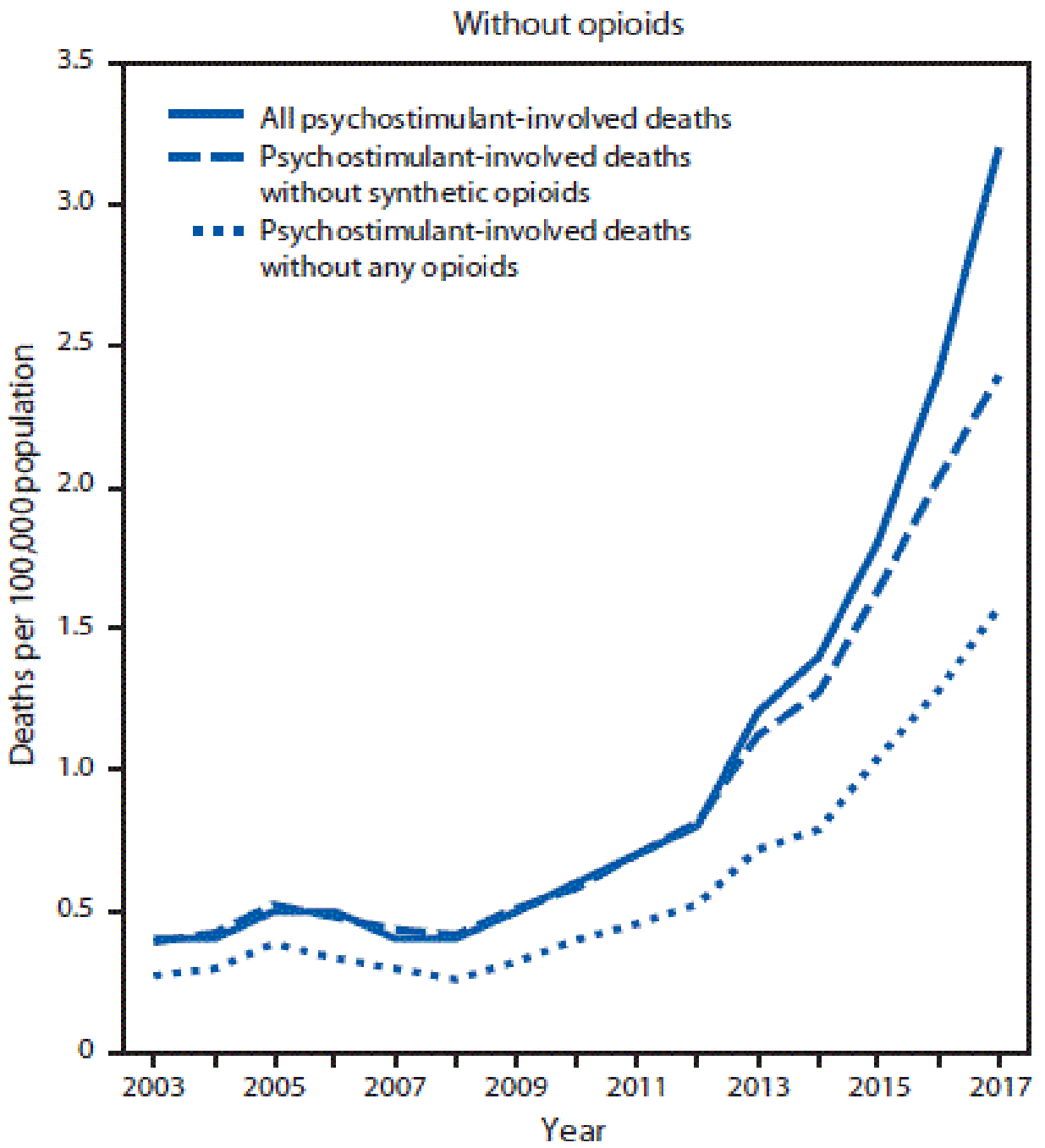
Ellis MS, et al. *Drug Alcohol Depend*. 2018;193:14-20.

Stimulant Overdose Deaths on the Rise



Sanger-Katz M. Bleak New Estimates in Drug Epidemic: A Record 72,000 Overdose Deaths in 2017. *The New York Times*. August 15, 2018.





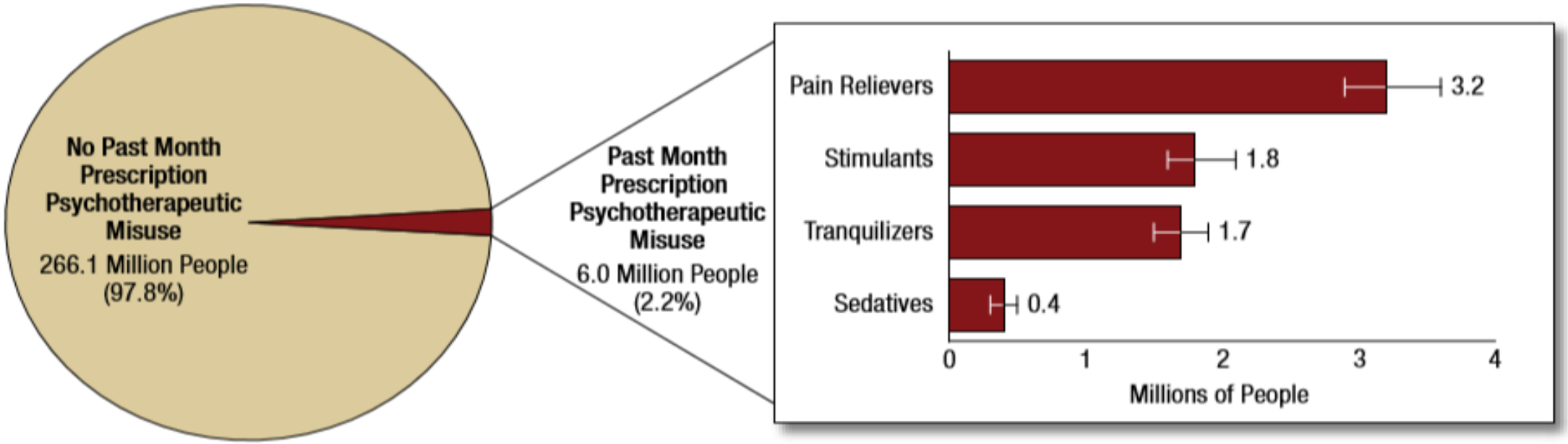
Kariisa M, et al. ***MMWR Morb Mortal Wkly Rep*. 2019;68(17):388-395.**

Rates of Prescription Stimulant Misuse

- Prescription: An estimate of 0.7% (= 1.8 million) of people aged ≥ 12 misused prescription stimulants (NSDUH, 2017)
  - 0.5% of adolescents aged 12 to 17
  - 2.1% of young adults aged 18 to 25
  - 0.5% of adults aged ≥ 26

Substance Abuse and Mental Health Services Administration. (2018). *Key substance use and mental health indicators in the United States: Results from the 2017 National Survey on Drug Use and Health* (HHS Publication No. SMA 18-5068, NSDUH Series H-53). Rockville, MD: Center for Behavioral Health Statistics and Quality, Substance Abuse and Mental Health Services Administration. www.samhsa.gov/data/sites/default/files/cbhsq-reports/NSDUHFFR2017/NSDUHFFR2017.htm. Accessed July 8, 2019.

Past Month Prescription Psychotherapeutic Misusers People Aged ≥ 12 (NSDUH, 2017)



Note: Estimated numbers of people refer to people aged 12 or older in the civilian, noninstitutionalized population in the United States. The numbers do not sum to the total population of the United States because the population for NSDUH does not include people aged 11 years or younger, people with no fixed household address (e.g., homeless or transient people not in shelters), active-duty military personnel, and residents of institutional group quarters, such as correctional facilities, nursing homes, mental institutions, and long-term care hospitals.

Note: The estimated numbers of past month misusers of different prescription psychotherapeutics are not mutually exclusive because people could have misused more than one type of prescription psychotherapeutic in the past month.

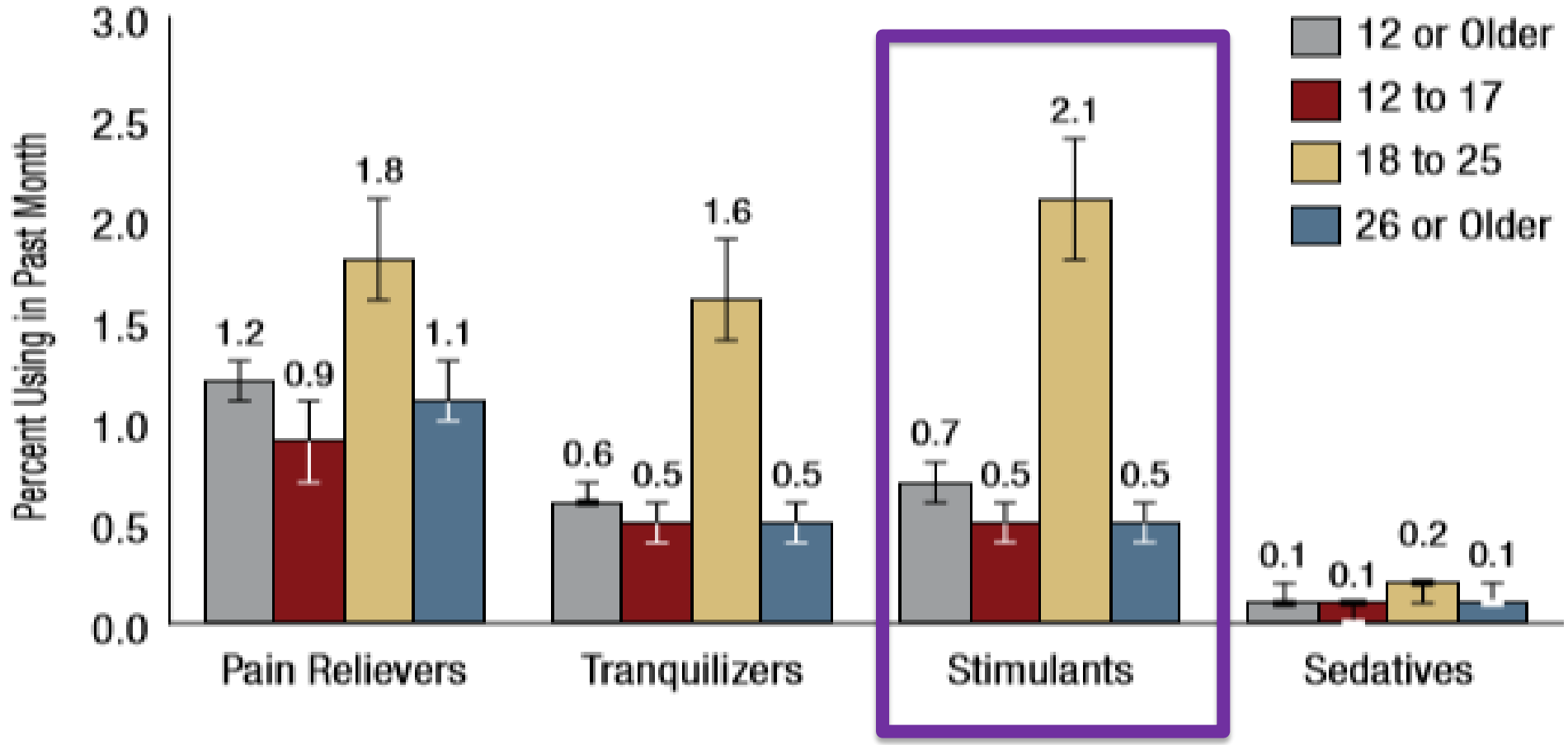
Substance Abuse and Mental Health Services Administration. (2018). *Key substance use and mental health indicators in the United States: Results from the 2017 National Survey on Drug Use and Health* (HHS Publication No. SMA 18-5068, NSDUH Series H-53). Rockville, MD: Center for Behavioral Health Statistics and Quality, Substance Abuse and Mental Health Services Administration. www.samhsa.gov/data/sites/default/files/cbhsq-reports/NSDUHFFR2017/NSDUHFFR2017.htm. Accessed July 8, 2019.

Rates of Prescription Stimulant Misuse: *College Students*

- An average of 17% of college students misuse stimulants
- Studies consistently confirmed that this misuse is motivated by cognitive and academic enhancement
  - Other less commonly endorsed motives include recreational reasons, weight loss, and curiosity
- A study examining a graduate students sample revealed a lifetime prevalence of 17.5%
- Risks predictive of misuse include symptoms of inattention, anxiety, stress, impulsivity, and restlessness

Benson K, et al. *Clin Child Fam Psychol Rev*. 2015;18(1):50-76. Weyandt LL, et al. *Exp Clin Psychopharmacol*. 2013;21(5):385-407. Verdi G, et al. *J Atten Disord*. 2016;20(9):741-753.

Past Month Prescription Stimulant Misuse by Age Group



Substance Abuse and Mental Health Services Administration. (2018). *Key substance use and mental health indicators in the United States: Results from the 2017 National Survey on Drug Use and Health* (HHS Publication No. SMA 18-5068, NSDUH Series H-53). Rockville, MD: Center for Behavioral Health Statistics and Quality, Substance Abuse and Mental Health Services Administration. www.samhsa.gov/data/sites/default/files/cbhsq-reports/NSDUHFFR2017/NSDUHFFR2017.htm. Accessed July 8, 2019.

Adverse Effects of Prescription Stimulant Misuse

- Initiation of stimulant use in young adults was associated with an increased risk of hospitalization for psychosis or mania
  - Among those that resumed use of stimulants, 40% were readmitted with recurrent psychosis or mania
- One study found a direct relationship between age at initiation of stimulant treatment and the frequency of SUD and ASPD
  - Lifetime rates of SUD were greater among patients with ADHD who initiated treatment between ages 8–12 (44%), as compared to patients who initiated treatment at age 6 or 7 (27%), or non-ADHD patients (29%)
  - This relationship mediated by development of ASPD

ADHD = attention-deficit/hyperactivity disorder; ASPD = antisocial personality disorder; SUD = substance use disorder.

Cressman AM, et al. *J Clin Psychopharmacol*. 2015;35(6):667-671. Mannuzza S, et al. *Am J Psychiatry*. 2008;165(5):604-609.

Clinical Effects of Stimulants

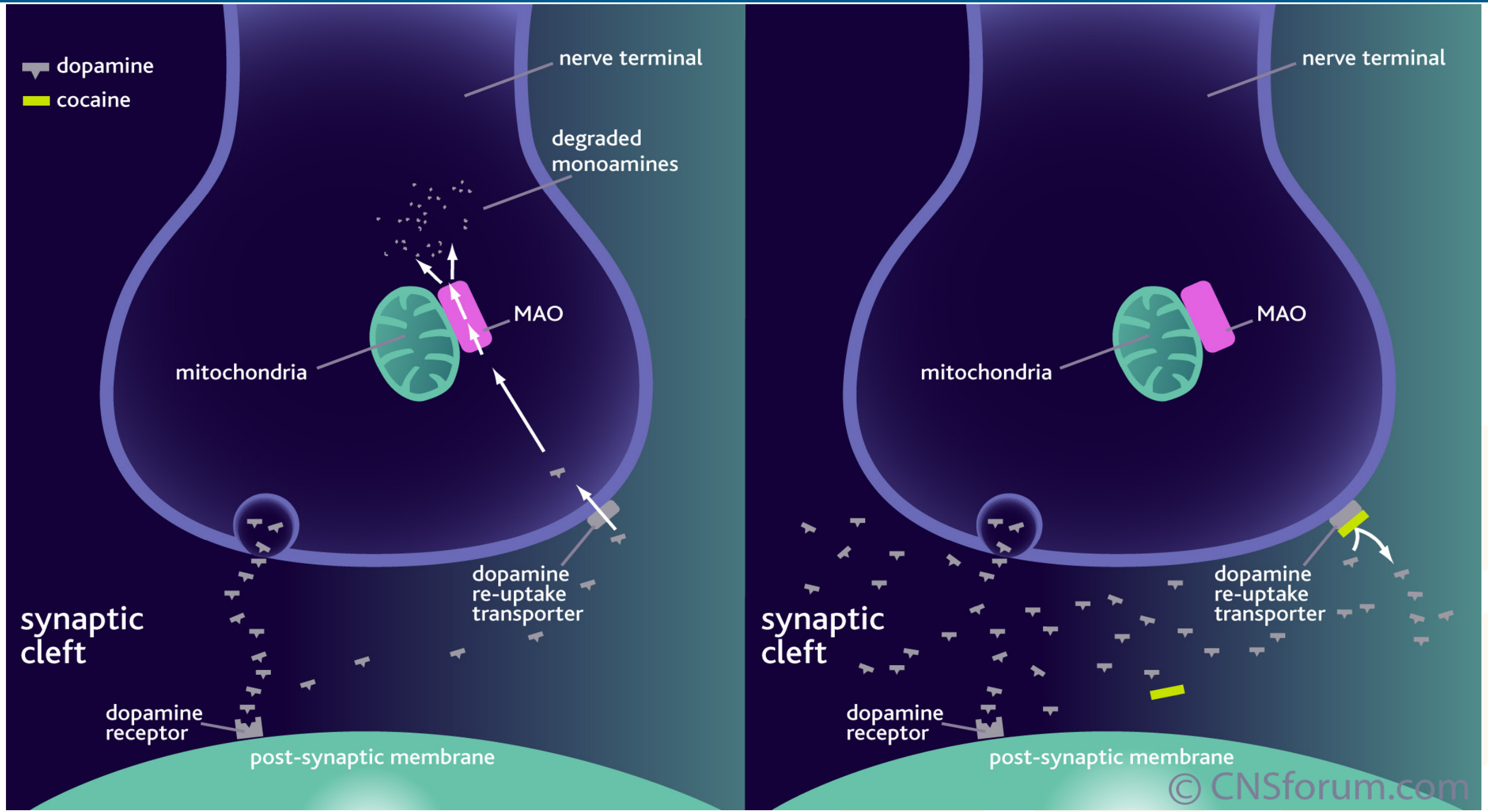
Clinical Effects of Stimulants

- Tachycardia, elevated blood pressure
- Increased alertness, energy
- Decreased appetite
- Insomnia
- Anxiety
- Hyperactivity/movement disorders
- Agitation

- Psychiatric: Depression, anxiety, psychosis (paranoia, AH), insomnia
- Medical: Arrhythmias, myocardial infarction, cerebrovascular accident, dental caries (methamphetamine), seizure

AH = auditory hallucinations.

Cocaine


dopamine
cocaine
nerve terminal
degraded monoamines
MAO
mitochondria
dopamine re-uptake transporter
synaptic cleft
dopamine receptor
post-synaptic membrane
nerve terminal
MAO
mitochondria
dopamine re-uptake transporter
synaptic cleft
dopamine receptor
post-synaptic membrane
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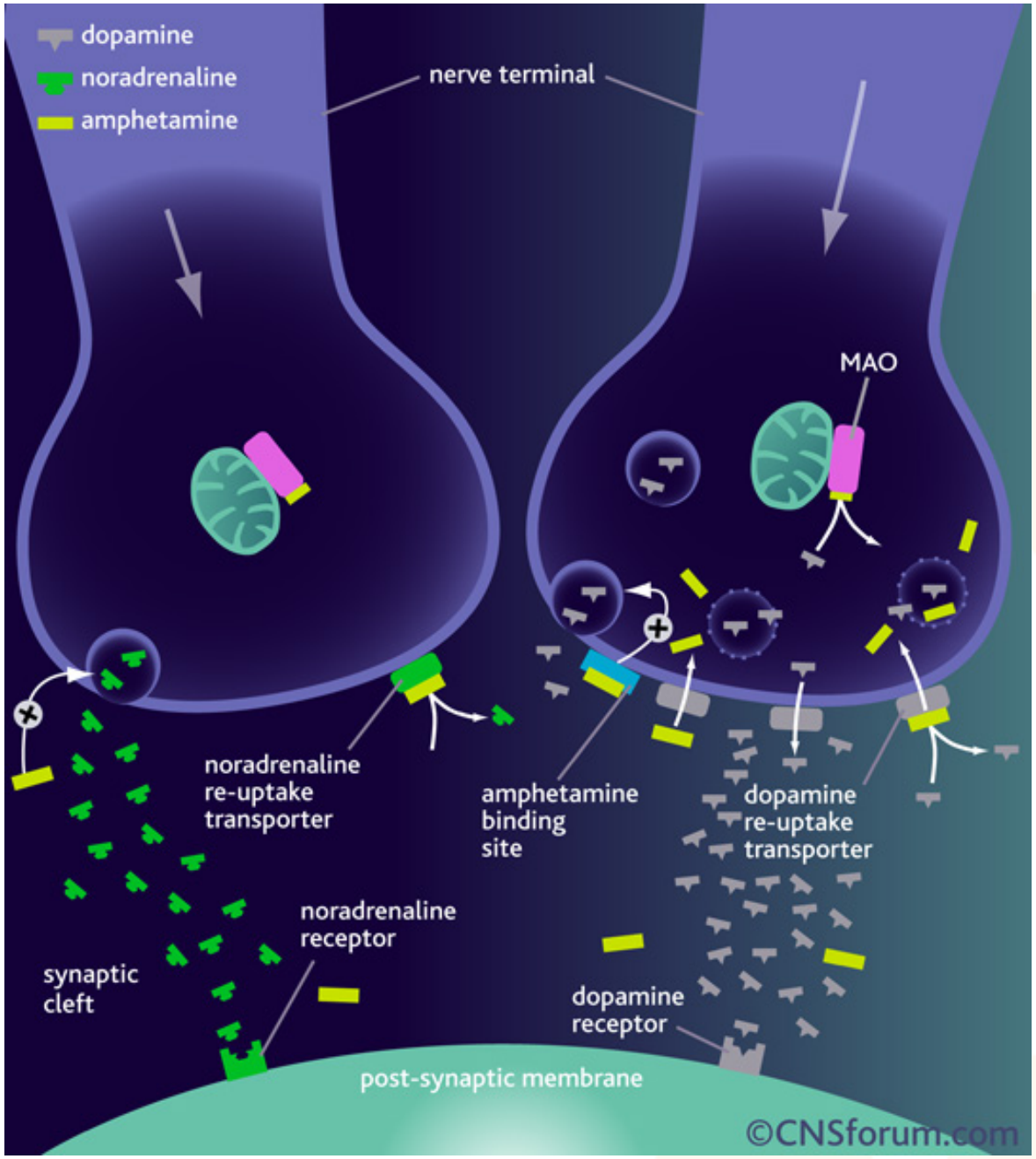
Methamphetamine


dopamine
noradrenaline
amphetamine
nerve terminal
MAO
noradrenaline
re-uptake
transporter
amphetamine
binding
site
dopamine
re-uptake
transporter
noradrenaline
receptor
synaptic
cleft
dopamine
receptor
post-synaptic membrane
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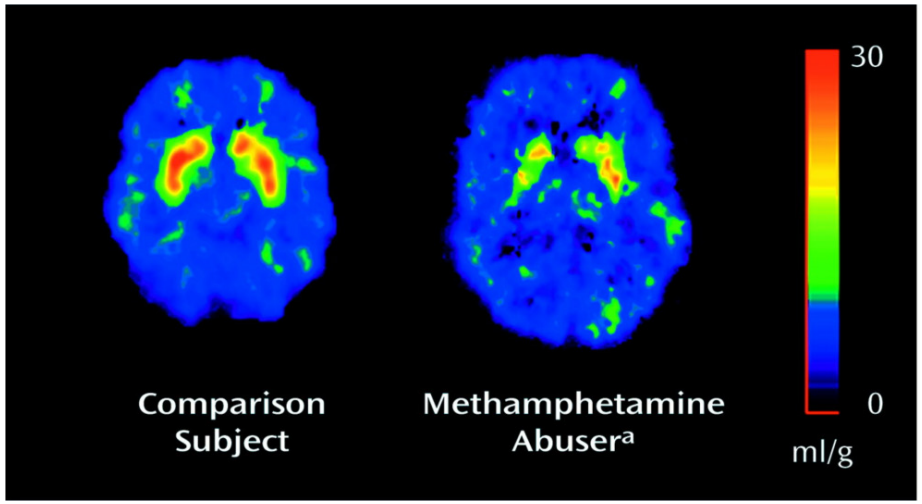
Stimulant Users Have Dysfunction in Brain Dopamine and Glutamate Systems

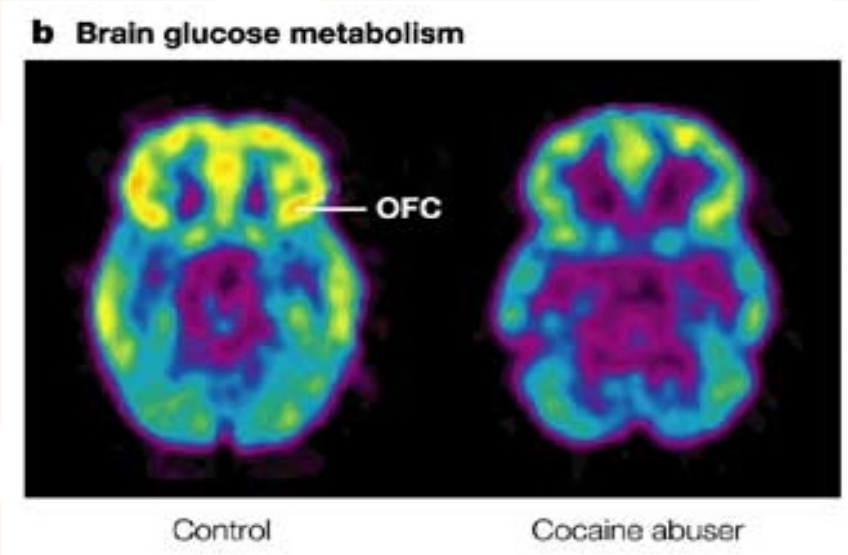


↓Dopamine transporters:

↓Ability to respond to non-drug rewards, ↑impulsivity, favor immediate > delayed reward

(b) ↓OFC function (glutamate):

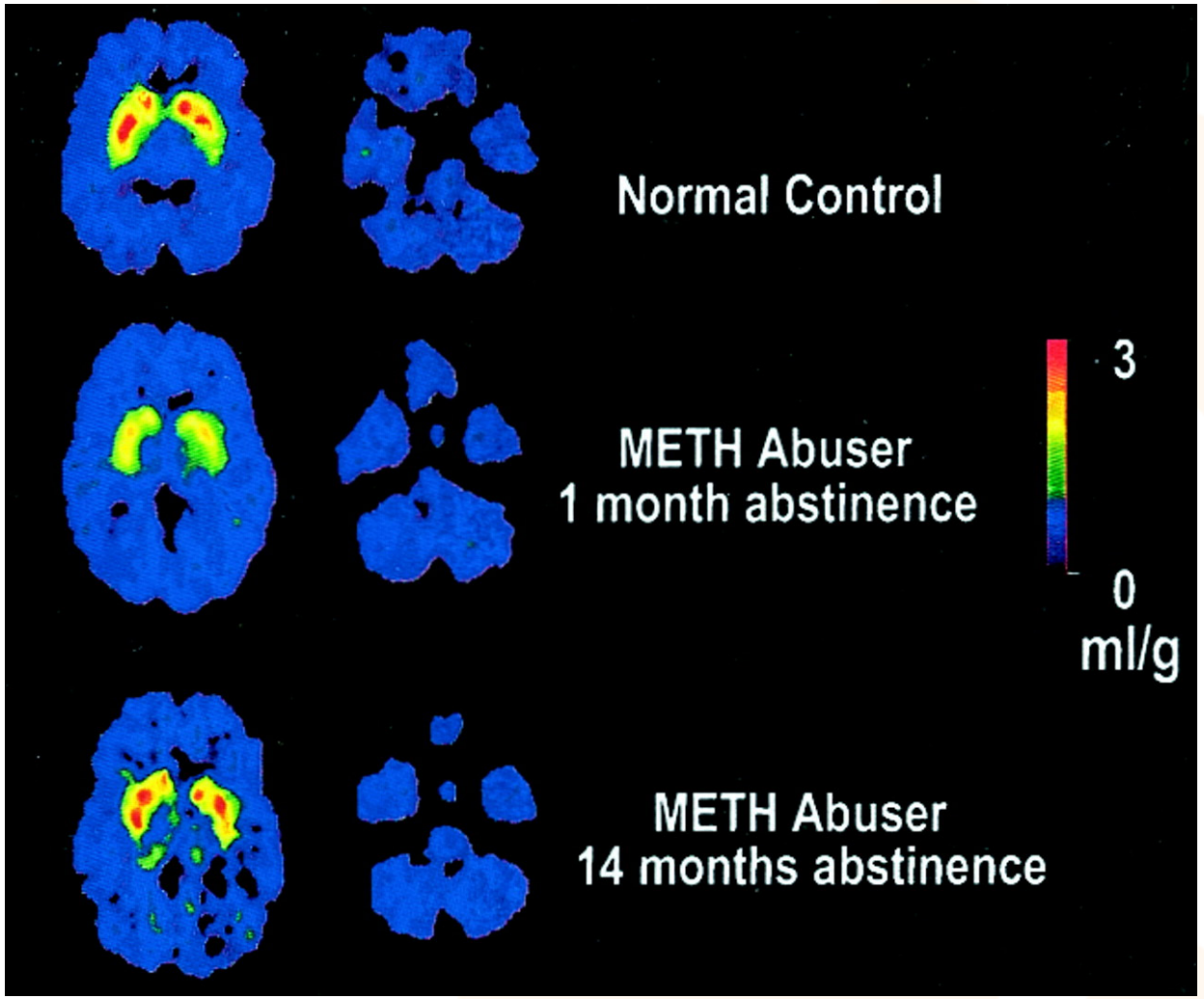
Poor decision-making, ↓ability to resist urges and cravings



OFC = orbitofrontal cortex.

Volkow ND, et al. *Am J Psychiatry*. 2001;158(3):377-382. Volkow ND, et al. *Nat Rev Neurosci*. 2004;5(12):963-970.

Recovery of Dopamine Transporter in Methamphetamine Users



Volkow ND, et al. *J Neurosci*. 2001;21(23):9414-9418.

Treatment of Cocaine and Methamphetamine Use Disorders

Behavioral Interventions

- Cognitive-behavioral therapy
- Matrix Model
- Contingency management
- Motivational enhancement therapy
- 12-Step facilitation

- Behavioral interventions may be combined with 12-Step support

- Consider level of care (eg, intensive outpatient, residential)

National Institute on Drug Abuse. *Principles of Drug Addiction Treatment: A Research-Based Guide* (Third Edition). January 17, 2018. www.drugabuse.gov/publications/principles-drug-addiction-treatment-research-based-guide-third-edition. Accessed August 5, 2019.

Medications for Methamphetamine Use Disorder

<u>Positive/Under Consideration</u>

- Bupropion (better in low-severity users)
- Mirtazapine
- Naltrexone
- Methylphenidate
  - D-amphetamine (craving/withdrawal)
- Topiramate* (better if abstinent at treatment entry)

Heinzerling KG, et al. *Addiction*. 2014;109(11):1878-1886. Colfax GN, et al. *Arch Gen Psychiatry*. 2011;68(11):1168-1175. Jayaram-Lindström N, et al. *Am J Psychiatry*. 2008;165(11):1442-1448. Tiihonen J, et al. *Am J Psychiatry*. 2007;164(1):160-162. Galloway GP, et al. *Clin Pharmacol Ther*. 2011;89(2):276-282. Elkashef A, et al. *Addiction*. 2012;107(7):1297-1306.

Medications for Methamphetamine Use Disorder (cont'd)

Negative Results

- Imipramine
- Desipramine
- Ondansetron
- Tyrosine
- Fluoxetine
- Sertraline
- Paroxetine
- Aripiprazole
- Gabapentin
- N-acetylcysteine
- Modafinil* (better in high-severity users)

Pharmacotherapy Evidence for Methamphetamine Use Disorder

- Underpowered studies, high attrition
- Bupropion may be more effective in individuals with lower use disorder severity
  - May be better in individuals with depression, males
- Low strength evidence that methylphenidate and topiramate may facilitate reduction in use
  - Topiramate better if negative urine screen at baseline

Chan B, et al. *Pharmacotherapy for Stimulant Use Disorders: A Systematic Review* [Internet]. Washington (DC): Department of Veterans Affairs (US); 2018 August. www.ncbi.nlm.nih.gov/books/NBK536789/. Accessed July 8, 2019.

Bupropion for Methamphetamine Use Disorder

Randomized trial of bupropion SR 150 mg twice daily vs placebo for 12 weeks in methamphetamine users with ***less than daily methamphetamine use***

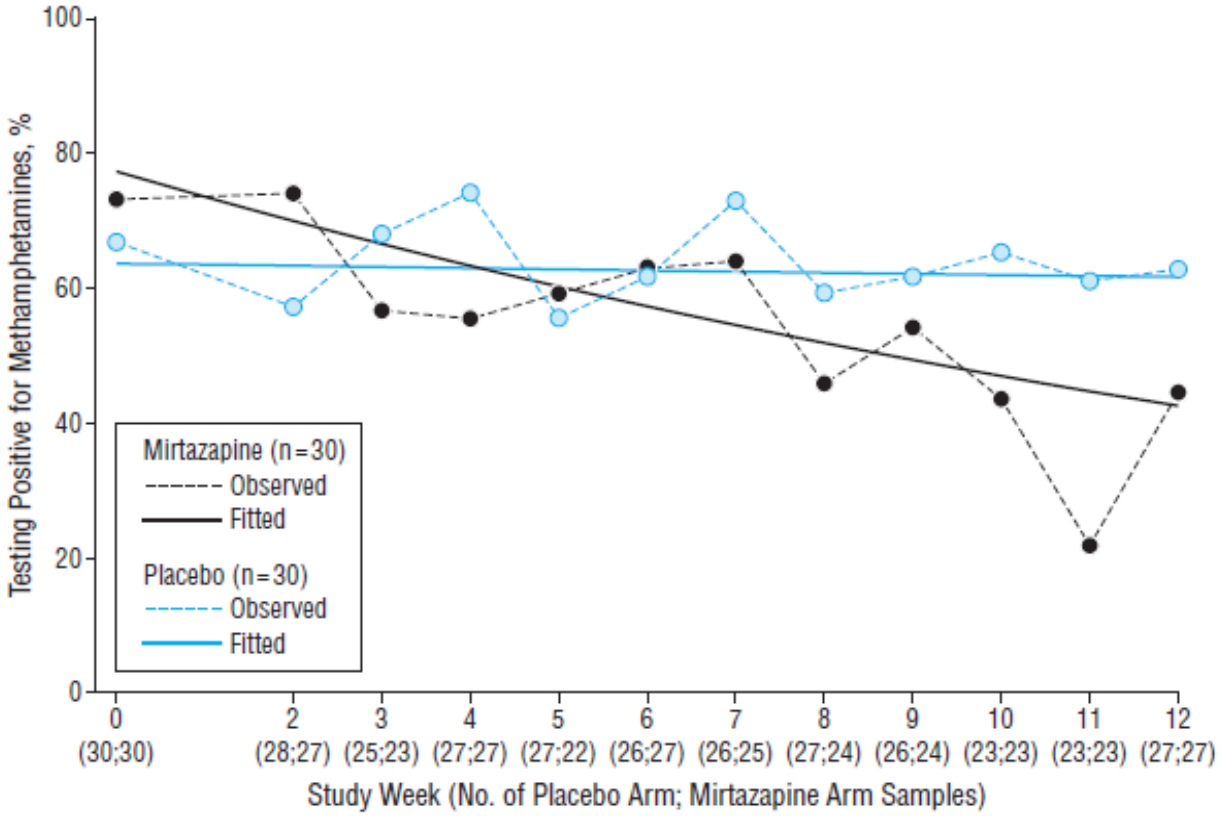
Total Sample	Bupropion (N=41)	Placebo (N=43)	*P*-value
End of treatment abstinence	29% (12)	14% (6)	.087

Only 32% (13/41) of bupropion participants were deemed medication adherent via week 6 plasma bupropion level. Adherence was strongly associated with end of treatment methamphetamine abstinence

Bupropion Only	Adherent (N=13)	Non-adherent (N=28)	*P*-value
End of treatment abstinence	54% (7)	18% (5)	.018

Heinzerling KG, et al. *Addiction*. 2014;109(11):1878-1886.

Mirtazapine for Methamphetamine Use Disorder



Observed and fitted weekly urinalysis results, according to treatment arm. Fitted trend lines are based on the primary outcome model.

MSM = men who have sex with men; NE = norepinephrine.

Colfax GN, et al. *Arch Gen Psychiatry*. 2011;68(11):1168-1175.

Summary

- 30 mg/day in methamphetamine-dependent MSM (N=60)
- Methamphetamine-positive urine test results lower for mirtazapine relative to placebo (*P*=.02)
- HIV risk behaviors also reduced on mirtazapine
- Mechanism: Enhance DA/NE via blocking presynaptic α_2-adrenergic and/or 5-HT_{2C} receptors?

Methylphenidate for Methamphetamine Use Disorder

- N=90 individuals seeking treatment for MUD
- 10 weeks active medication (MPH titrated to 54 mg/day vs placebo)
  - Followed by 4-week single-blind placebo phase
- CBT platform with motivational incentives (MA(-) UDS)
- MPH was associated with significantly fewer self-reported days of MA use over the active treatment period than placebo in MA users with > 10 days use in past 30 days at baseline (not for 1° outcome)
- MPH group reduced MA use > placebo from baseline to end of active phase (6.5 vs 3.5 days)
- No difference in proportion of (+)UDS across active medication period
- MPH group had fewer MA(+) UDS at week 14
- MPH group had lower craving scores at weeks 10 and 14

CBT = cognitive-behavioral therapy; MA = methamphetamine; MPH = methylphenidate; UDS = urine drug screen.

Ling W, et al. *Addiction*. 2014;109(9):1489-1500.

Naltrexone for Methamphetamine Use Disorder

- Naltrexone shown to reduce subjective effects of MA and relapse to MA use
- NIDA CTN pilot study: Open-label naltrexone XR + bupropion in 49 severe MA users for 8 weeks yielded 11 “responders” (6/8 MA(-) UDS in last 4 weeks of medications)
- Follow-up RCT (NIDA CTN) now underway

NIDA CTN = National Institute of Drug Abuse Clinical Trials Network; RCT = randomized controlled trial.

Jayaram-Lindström N, et al. *Am J Psychiatry*. 2008;165(11):1442-1448. Mooney LJ, et al. *J Addict Med*. 2016;10(4):236-243.

Medications for Cocaine Use Disorder

Positive/Under Consideration

- Topiramate*
- Modafinil*
- Bupropion*
- Amphetamine salts*
- Disulfiram (mixed results, worse retention)
- Propranolol (withdrawal)
- Buprenorphine + naltrexone

Medications for Cocaine Use Disorder (cont'd)

<u>(Mostly) Negative</u>

- Gabapentin
- Aripiprazole
- Olanzapine
- Tiagabine
- Buspirone
- Desipramine*
- Amantadine*
- TA-CD vaccine
- Baclofen*
- GVG (vigabatrin)
- N-acetylcysteine

Pharmacotherapy Evidence for Cocaine Use Disorder

- Limited/insufficient evidence that most medication classes do not improve abstinence, use, or Tx retention
- Limited power, methodological deficiencies, high attrition
- Low strength evidence for increasing abstinence at ≥ 2 weeks: psychostimulant class, bupropion, topiramate
  - Stimulants: dexamphetamine, mixed amphetamine salts
- No difference in cocaine use outcomes w/ or w/o ADHD
- Antidepressants, anticonvulsants (except topiramate), and neuroleptics do not improve abstinence, use, or retention
- SSRIs and disulfiram: Lower retention than placebo
- Ability to achieve sustained abstinence or produce a cocaine(-) UDS may be a good predictor of treatment success

SSRI = selective serotonin reuptake inhibitor.

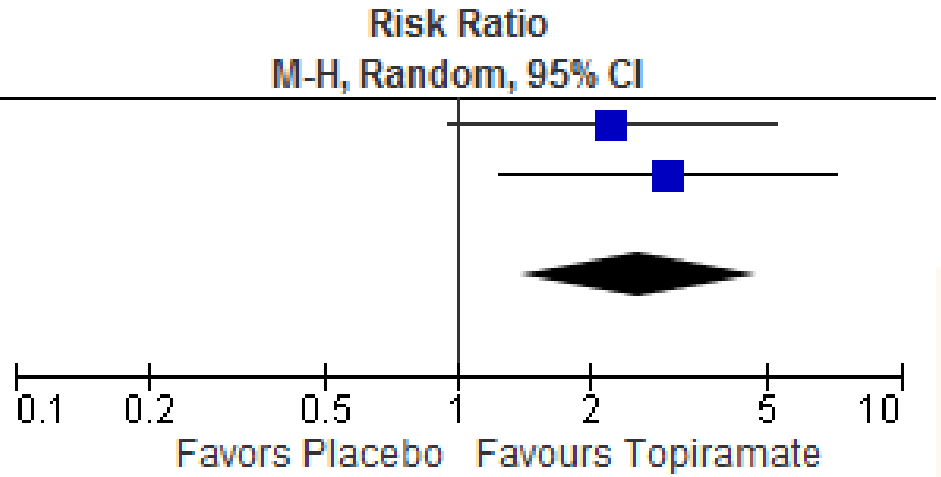
Chan B, et al. *Pharmacotherapy for Stimulant Use Disorders: A Systematic Review* [Internet]. Washington (DC): Department of Veterans Affairs (US); 2018 August. www.ncbi.nlm.nih.gov/books/NBK536789/. Accessed July 8, 2019.

Abstinence for 2+ Continuous Weeks in RCTs of Topiramate vs Placebo for Cocaine Use Disorder

Study or Subgroup	Topiramate Events	Topiramate Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
Kampman, 2004 - 13 wk	10	17	5	19	51.7%	2.24 [0.95, 5.24]
Kampman, 2013 - 13 wk	17	83	6	87	48.3%	2.97 [1.23, 7.17]
Total (95% CI)		**100**		**106**	**100.0%**	**2.56 [1.39, 4.73]**
Total events	27		11			

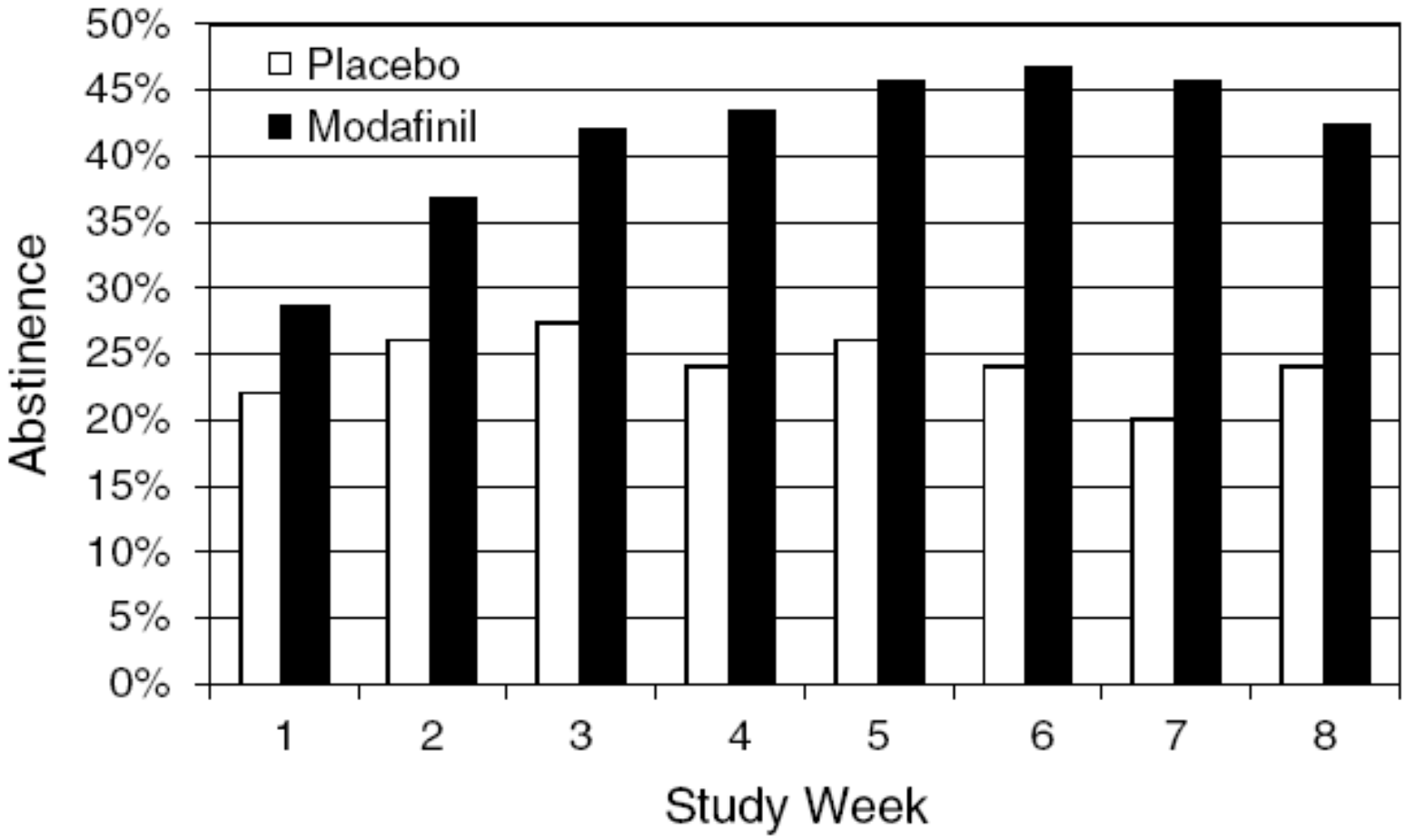
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.22$, df = 1 (P = 0.64); $I^2 = 0\%$

Test for overall effect: Z = 3.02 (P = 0.003)



Chan B, et al. *Pharmacotherapy for Stimulant Use Disorders: A Systematic Review* [Internet]. Washington (DC): Department of Veterans Affairs (US); 2018 August. www.ncbi.nlm.nih.gov/books/NBK536789/. Accessed July 8, 2019.

Modafinil for Cocaine Use Disorder



Dackis CA, et al. *Neuropsychopharmacology*. 2005;30(1):205-311.

Modafinil and Alcohol Comorbidity

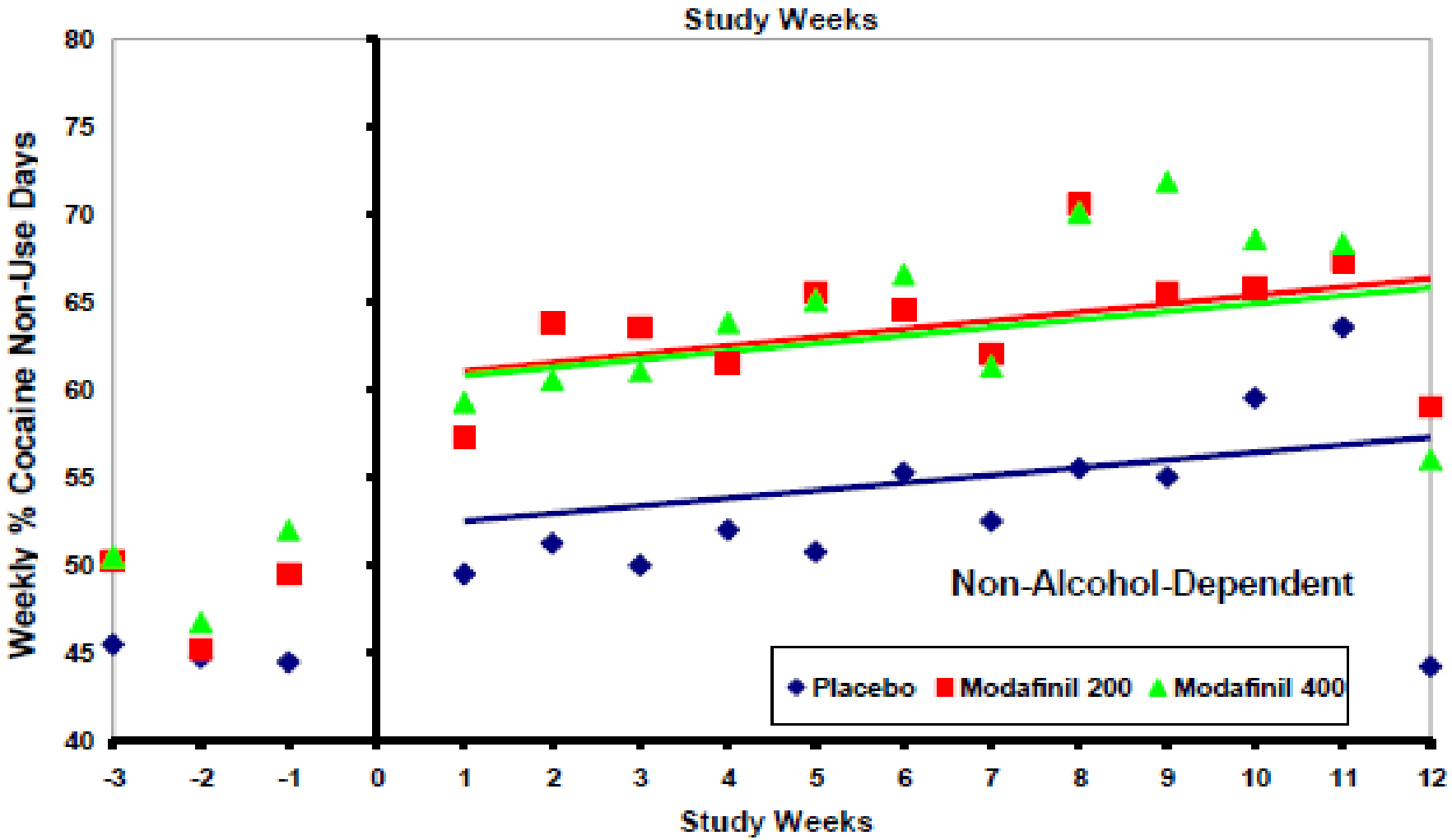
- Dackis study excluded individuals with a history of or current alcohol dependence

- Alcohol is co-used with cocaine in the majority of cocaine users in the United States
  - Range of reported co-use is 60% to 80%

- NIDA replication study – 6 centers
- Enrolled 210 participants with cocaine dependence w/ and w/o alcohol dependence
  - Modafinil 200 mg vs 400 mg vs placebo

Anderson AL, et al. *Drug Alcohol Depend*. 2009;104(1-2):133-139.

Weekly Non-Use Days: Non-Alcohol Dependent



Anderson AL, et al. *Drug Alcohol Depend*. 2009;104(1-2):133-139.

ER-Mixed Amphetamine Salts + Topiramate for Cocaine Use Disorder

- N=81 adults with CUD
- Randomized to MAS-ER + topiramate vs placebo for 12 weeks
- MAS-ER titrated to 60 mg/day; topiramate titrated to 150 mg BID
- Primary outcome of 3 consecutive weeks abstinence was significant for MAS-ER + topiramate
  - Effect moderated by days of cocaine use at baseline

MAS-ER = extended-release mixed amphetamine salts.

Mariani JJ, et al. *Biol Psychiatry*. 2012;72(11):950-956.

Summary of Off-Label Pharmacotherapy Options

- ***Cocaine***: topiramate, psychostimulants (eg, modafinil 200–300 mg/day [*non-alcohol use disorder], MAS-ER 60 mg/day, bupropion 300 mg/day)

- ***Methamphetamine***: bupropion 300 mg/day, topiramate 300 mg/day, naltrexone, mirtazapine 30 mg/day, methylphenidate 54 mg/day

- **Safety considerations**: Seizure threshold, H/O prescription stimulant use disorder, medical/psychiatric/substance comorbidities

Clinical Conundrums in Stimulant Use Disorder Treatment

- Varying levels of severity of use (eg, frequency, duration, route)
- Primary prescription stimulant use disorder vs methamphetamine vs cocaine
- Co-occurring SUDs (eg, alcohol, opioids)
- Co-occurring psychiatric disorders
- Is pharmacotherapy appropriate for all patients with stimulant use disorder seeking treatment?

Treatment of Patients with ADHD and Stimulant Use Disorder

International Consensus Statement on Screening, Diagnosis and Treatment of Substance Use Disorder Patients with Comorbid ADHD (2018)

- Conclusions based primarily on scientific evidence from available publications (n=212)
  - When scientific evidence was lacking, a consensus was sought from the opinions of experts in the field
- ADHD is associated with an increased risk of developing SUD later in life
- A meta-analysis of 29 studies showed 23.1% of adult patients with SUD also had ADHD
- Age, gender, ethnicity, and primary substance do not seem to systematically impact prevalence rate of ADHD in SUD patients

Crunelle CL, et al. *Eur Addict Res*. 2018;24(1):43-51.

ADHD-SUD Comorbidity is Associated with Reduced Effectiveness of Standard Treatment

- Earlier onset and faster transition to SUD
- More complex and chronic patterns of use
  - Increased polysubstance use
- Greater comorbidity with other psychiatric conditions
  - Antisocial and borderline personality disorders
  - Anxiety disorders
  - Bipolar disorders
  - Posttraumatic stress disorder

Crunelle CL, et al. *Eur Addict Res*. 2018;24(1):43-51.

ADHD-SUD Comorbidity is Associated with Greater Complexity and Treatment Challenges

- More frequent treatment
  - More difficulties with abstinence
  - Reduced quality of life
  - More professional, social, and personal problems
- Lower effectiveness of standard-dose pharmacotherapy for ADHD

Crunelle CL, et al. *Eur Addict Res*. 2018;24(1):43-51.

Medication Effectiveness in Reducing ADHD Symptoms in ADHD-SUD Comorbidity

- Mean standardized effect size 0.40–0.50
  - Studies showed promise with regard to SUD outcomes in secondary analyses
- 2 studies with higher doses of methylphenidate (up to 180 mg/day) showed a decrease in ADHD symptoms and a decrease in the reinforcing effects and the use of cocaine and amphetamines (and other drugs) in adult stimulant-dependent ADHD patients

Crunelle CL, et al. *Eur Addict Res*. 2018;24(1):43-51. Konstenius M, et al. *Addiction*. 2014;109(3):440-449. Levin FR, et al. *JAMA Psychiatry*. 2015;72(6):593-602.

Medication Effectiveness in Reducing ADHD Symptoms in ADHD-SUD Comorbidity (cont'd)

- Robust doses of MAS-ER (60 and 80 mg/day) showed substantial reductions in both ADHD and substance use in cocaine-dependent patients with ADHD
- Atomoxetine resulted in a significant reduction on ADHD symptoms, and was associated with a decrease in alcohol craving and consumption
- Some evidence for the effectiveness of bupropion to reduce ADHD symptoms in patients with ADHD-SUD
  - However, results have been contradicted in small controlled studies showing no effect over placebo

Crunelle CL, et al. *Eur Addict Res*. 2018;24(1):43-51. Levin FR, et al. *JAMA Psychiatry*. 2015;72(6):593-602. Wilens TE, et al. *Drug Alcohol Depend*. 2008;96(1-2):145-154. Levin FR, et al. *Drug Alcohol Depend*. 2006;81(2):137-148.

Medication Effectiveness in Reducing ADHD Symptoms in ADHD-SUD Comorbidity (cont'd)

- Guanfacine XR is an effective and approved treatment for children and adolescents with ADHD
  - Mild-moderate adverse effects; most common effect is sedation
- Preliminary evidence shows that guanfacine may be a well-tolerated treatment option for adult ADHD
  - More research needed
- Pemoline was also shown to have positive effects on ADHD, but not on drug use

Faraone SV, et al. *Clin Ther*. 2013;35(11):1778-1793. Taylor FB, et al. *J Clin Psychopharmacol*. 2001;21(2):223-228. Crunelle CL, et al. *Eur Addict Res*. 2018;24(1):43-51.

Prescribing Stimulants to Individuals with Substance Use Disorders Remains Controversial

- Many clinicians are reluctant to prescribe standard ADHD treatment in individuals with SUD
  - There is the clear risk of misuse and diversion of prescription stimulants
  - Prior studies have not demonstrated severe complications or increases in substance use when prescribing central stimulants in this patient population
  - However, study designs do not always replicate real-world practice standards (eg, visit frequency)
- Adverse events are not increased in ADHD patients with SUD compared to when giving stimulants to ADHD patients without SUD

Crunelle CL, et al. *Eur Addict Res*. 2018;24(1):43-51.

Prescribing Stimulants to Individuals with Substance Use Disorders Remains Controversial (cont'd)

- Long-acting formulations, particularly osmotic-release oral system formulations of methylphenidate and lisdexamfetamine, have considerably lower rates of misuse and diversion compared to immediate-release preparations
  - Risk of abuse becomes relatively lower when medications are prescribed under monitored conditions
- Treatment of ADHD can be useful to reduce ADHD symptoms without worsening the SUD and should not be avoided

Crunelle CL, et al. *Eur Addict Res*. 2018;24(1):43-51. Mariani JJ, et al. *Am J Addict*. 2007;16 Suppl 1:45-54.

Medication Has More Positive Effects When Combined with Psychotherapy

- Combining pharmacotherapy (for ADHD and SUD) with a nonpharmacologic intervention that targets both the ADHD and SUD, such as an integrated CBT, is warranted
  - Clinicians should consider therapy with a focus on overlapping symptoms as part of a multimodal treatment approach
- ADHD pharmacotherapy by itself is generally not effective in reducing the use of substances and is associated with a higher frequency of adverse effects and treatment discontinuation

Crunelle CL, et al. *Eur Addict Res*. 2018;24(1):43-51.

ADHD Treatment Considerations in Substance Use Disorders

- Atomoxetine
- Methylphenidate, MAS-ER, lisdexamfetamine
- Bupropion
- Tricyclic antidepressants
- Guanfacine XR

- Differences when primary SUD is stimulant use disorder vs other?
- If H/O prescription stimulant use disorder, risk of prescription stimulants likely outweigh potential benefits of ADHD treatment
- Role of behavioral treatments

Conclusions

- Higher dose and longer-acting formulation stimulants can be effective in treating ADHD in those with ADHD-SUD
- However, there is a clear risk of misuse and diversion of stimulants
- 2 groups at substantial risk are adolescents and young adults
- When potential risks outweigh benefits, or as initial trial, consider non-addictive ADHD pharmacotherapy and/or behavioral treatment

Methamphetamine: Case #1

- 27-year-old male with a history of bipolar disorder and MUD, severe (H/O nearly daily use via smoking since age 20)
- Intermittent binge alcohol use
- History of prior psychiatric admissions, suicide attempt 3 years ago by medication overdose, and history of prior treatment with mood stabilizers (lamotrigine, valproic acid)
- Enrolled in a 3-day/week intensive outpatient treatment program
- Maintained sobriety for 2 months, then no-showed for 3 weeks
- Now returns reporting insomnia, racing thoughts, and intermittent AH of whispers; concerned that he is becoming “manic”
- Has visible excoriations on face; describes episodes of picking due to sensations of “pebbles” under his skin
- UDS(+) for methamphetamine

Cocaine: Case #2

- 35-year-old attorney with history of heavy binge alcohol use and periodic cocaine use during times of stress/work demands
- Has used cocaine to complete work deadlines and minimize need for sleep
- More recently has increased cocaine use to 3 to 4 days/week
- Missing work more frequently and having greater conflict at home with spouse
- On evaluation reports increasing symptoms of depression, anhedonia, insomnia, irritability, and anxiety