FDA's Integrated Approach to Addressing Polysubstance Use and the Drug Overdose Crisis

Marta Sokolowska, PhD

Associate Director for Controlled Substances, Office of the Center Director,

Center for Drug Evaluation and Research, U.S. Food and Drug Administration

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Disclaimer

- This presentation reflects the views of the author and should not be construed to represent FDA's views or policies.

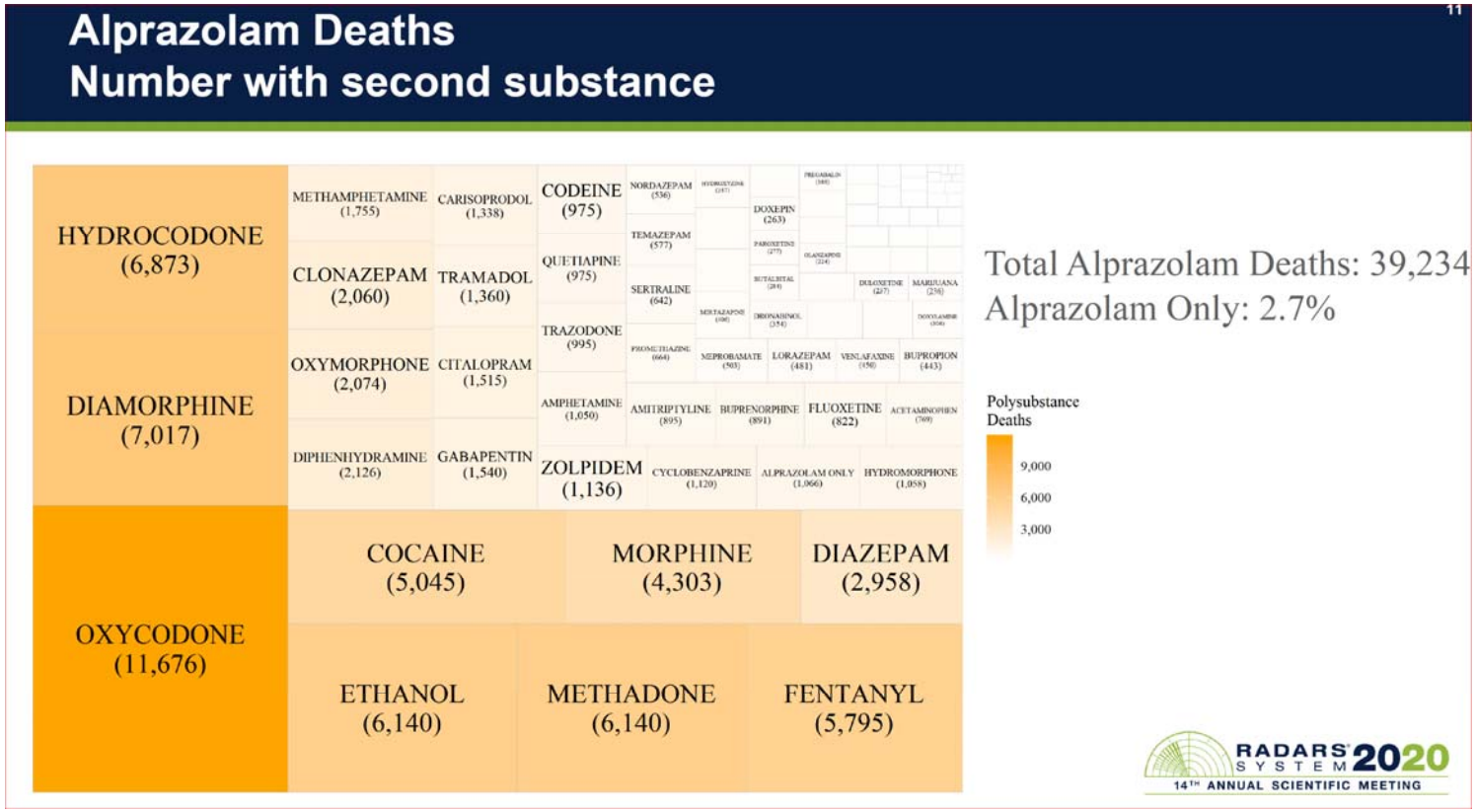
Overview of talk

- Selection of polysubstance use literature
  - Focus on benzodiazepines and stimulants

- FDA's integrated approach to accelerating treatment development

Benzodiazepines

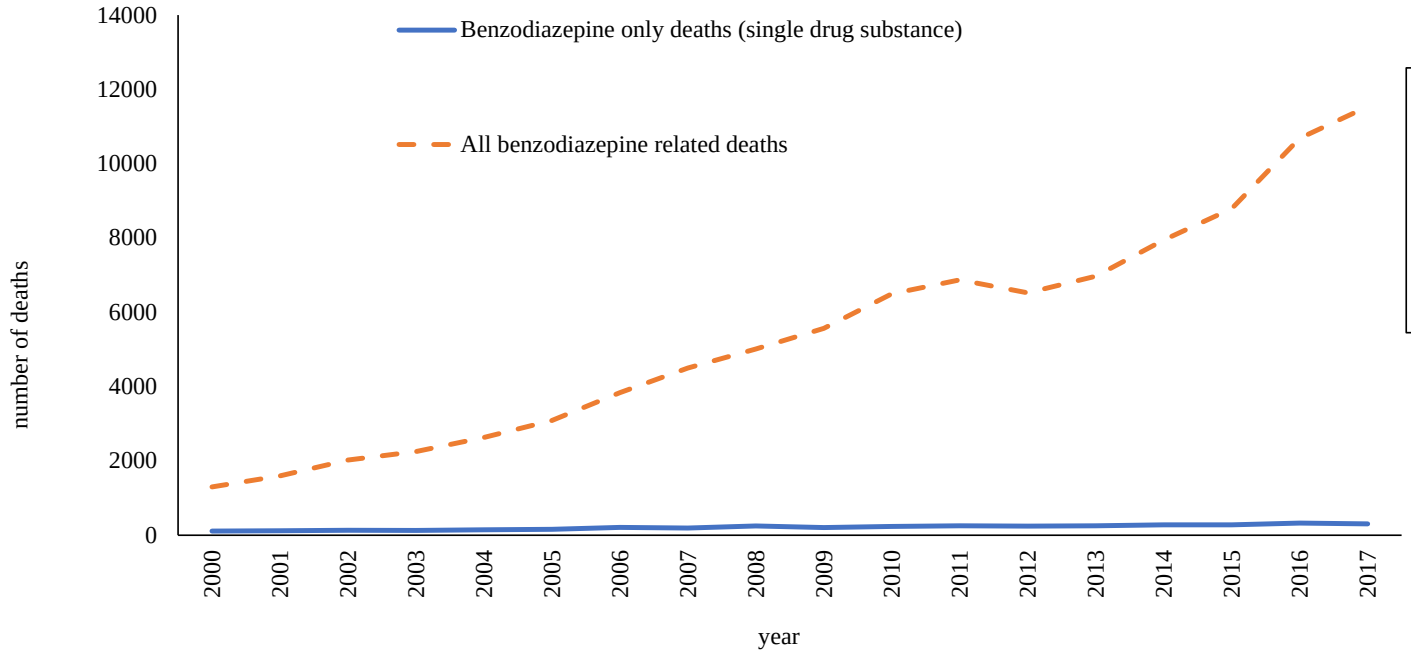
Thinking back to the RADARS System 2020 Scientific Meeting



Source: Black, J. One Drug? Two Drugs? Polydrug Mortality Is More Common Than We Think. RADARS System 2020 14th Annual Scientific Meeting. https://www.radars.org/system/events/RADARS%20System%202020%20Annual%20Meeting_Black%20Polydrug%20Mortality.pdf.tmp

Most fatal benzodiazepine overdoses are polysubstance cases

Annual number of deaths involving benzodiazepines, 2000-2017



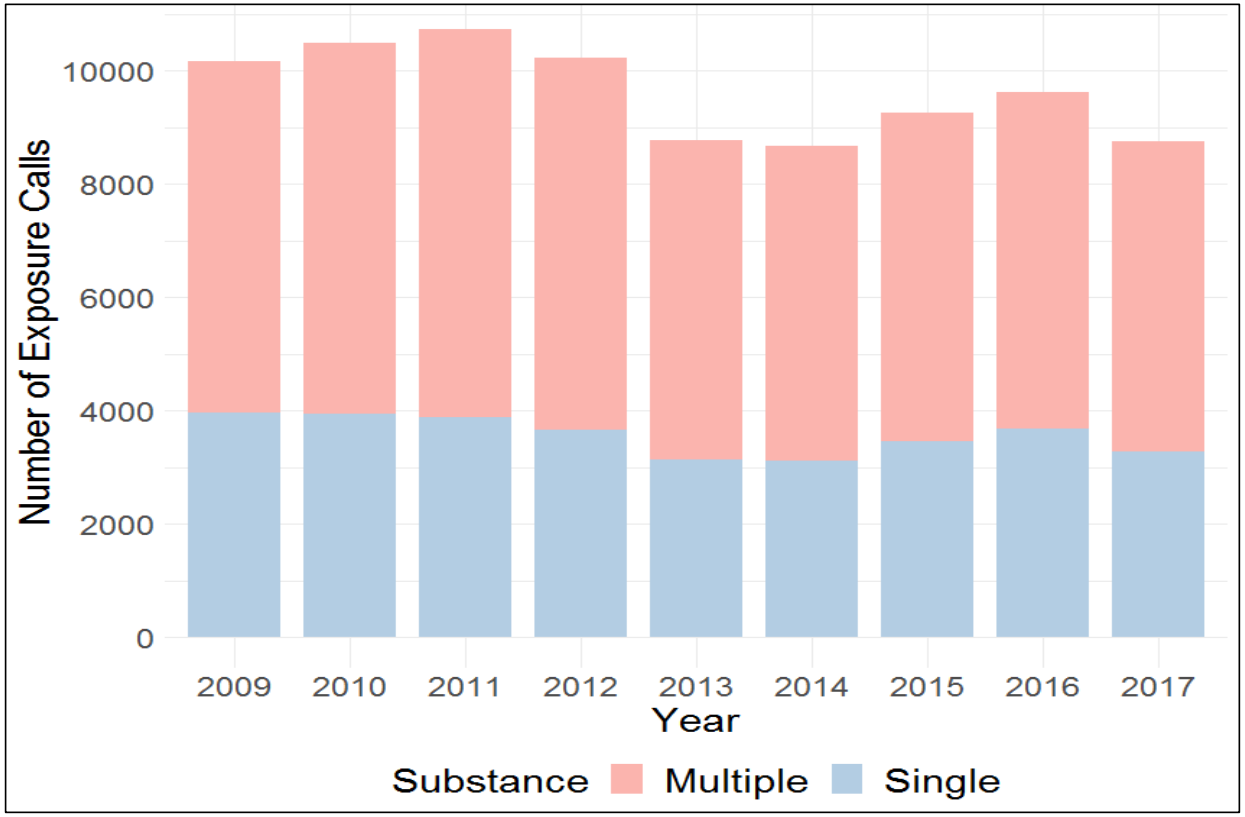
- 55.4% of benzo-involved deaths involved Rx opioids
- 9.7% involved ONLY benzos and Rx opioids

[a]Single drug substance defined by ICD-10 codes T36.0 to T50.9, does not involve alcohol (T51.0)
[b]drug poisoning underlying cause of death ICD-10 codes: X40-X44, X60-X64, X85, Y10-Y14

Source: National Vital Statistics System- Mortality (NVSS-M) 2000-2017

Poison Control Center Data

Number of cases involving benzodiazepine abuse or misuse, single and multiple-substances, 2009-2017



63% multi-substance calls

Most common concomitant substances:

- **Rx opioids**
- **Alcohol**
- **Stimulants**

Medical outcomes more severe than benzo single-substance calls

 Source: FDA Analysis of National Poison Data System (NPDS) 2009-2017

Benzodiazepine drug class: Drug Safety Communication – Boxed Warning updated to improve safety (Sept 2020)

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WARNING: RISKS FROM CONCOMITANT USE WITH OPIOIDS

Concomitant use of benzodiazepines and opioids may result in profound sedation, respiratory depression, coma, and death *[see Warnings, Drug Interactions]*.

- Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate.
- Limit dosages and durations to the minimum required.
- Follow patients for signs and symptoms of respiratory depression and sedation.

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tablets, USP

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WARNING: RISKS FROM CONCOMITANT USE WITH OPIOIDS; ABUSE, MISUSE, AND ADDICTION; and DEPENDENCE AND WITHDRAWAL REACTIONS

- **Concomitant use of benzodiazepines and opioids may result in profound sedation, respiratory depression, coma, and death. Reserve concomitant prescribing of these drugs for patients for whom alternative treatment options are inadequate. Limit dosages and durations to the minimum required. Follow patients for signs and symptoms of respiratory depression and sedation (see WARNINGS and PRECAUTIONS).**
- **The use of benzodiazepines, including XANAX, exposes users to risks of abuse, misuse, and addiction, which can lead to overdose or death. Abuse and misuse of benzodiazepines commonly involve concomitant use of other medications, alcohol, and/or illicit substances, which is associated with an increased frequency of serious adverse outcomes. Before prescribing XANAX and throughout treatment, assess each patient's risk for abuse, misuse, and addiction (see WARNINGS).**
- **The continued use of benzodiazepines, including XANAX, may lead to clinically significant physical dependence. The risks of dependence and withdrawal increase with longer treatment duration and higher daily dose. Abrupt discontinuation or rapid dosage reduction of XANAX after continued use may precipitate acute withdrawal reactions, which can be life-threatening. To reduce the risk of withdrawal reactions, use a gradual taper to discontinue XANAX or reduce the dosage (see DOSAGE AND ADMINISTRATION and WARNINGS).**

Source: https://www.fda.gov/safety/medical-product-safety-information/benzodiazepine-drug-class-drug-safety-communication-boxed-warning-updated-improve-safe-use

Psychostimulants:

Nonmedical Use (NMU) and Use Disorder

Emergency department visits involving nonmedical use of pharmaceutical products, 2016

Table 2. ED Visits Due to Nonmedical Use of Pharmaceuticals, by Category, 2016[a]

	Implicated alone or with other substances,[b] annual national estimate[d]		Implicated alone without other substances,[c] annual national estimate[e]		
Category	***n***	**% total visits (95% CI)**	***n***	**% total visits (95% CI)**	**% category (95% CI)**
Benzodiazepines	167,845	46.9 (42.5, 51.2)	23,335	6.5 (5.1, 7.9)	13.9 (10.9, 16.9)
Prescription opioids	129,863	36.2 (30.8, 41.7)	40,499	11.3 (8.6, 14.0)	31.2 (26.2, 36.1)
Antidepressants	24,350	6.8 (5.5, 8.1)	6,015	1.7 (1.1, 2.3)	24.7 (18.7, 30.7)
Cough/cold or antihistamines	23,966	6.7 (5.8, 7.6)	9,675	2.7 (2.0, 3.4)	40.4 (32.2, 48.5)
Nonopioid analgesics	23,758	6.6 (5.4, 7.9)	12,391	3.5 (2.6, 4.3)	52.2 (45.5, 58.8)
Hypnotics (non-benzodiazepine)	16,899	4.7 (3.8, 5.7)	2,374	0.7 (0.4, 1.0)	14.1 (7.8, 20.3)
Antipsychotics	15,874	4.4 (3.4, 5.5)	4,995	1.4 (1.0, 1.8)	31.5 (25.6, 37.3)
Muscle relaxants	14,731	4.1 (3.2, 5.0)	3,114	0.9 (0.5, 1.2)	21.1 (13.4, 28.9)
Gabapentinoids	11,669	3.3 (2.3, 4.2)	—	—	—
Stimulants	10,999	3.1 (1.8, 4.4)	3,677[f]	1.0 (0.4, 1.7)	33.4 (22.1, 44.8)
Antihypertensives	7,824	2.2 (1.6, 2.8)	2,958	0.8 (0.5, 1.1)	37.8 (25.6, 50.0)
Anticonvulsants	4,828	1.3 (0.9, 1.8)	1,966[f]	0.5 (0.2, 0.8)	40.7 (24.0, 57.4)
Antibiotics	4,278	1.2 (0.8, 1.6)	2,915	0.8 (0.5, 1.2)	68.1 (50.8, 85.5)
Other pharmaceuticals[g]	16,775	4.7 (3.9, 5.4)	6,978	1.9 (1.5, 2.4)	41.6 (33.1, 50.1)
Total	358,247	100 (N/A)	122,195	34.1 (30.5, 37.7)	N/A

[a]Estimates are from the National Electronic Injury Surveillance System—Cooperative Adverse Drug Event Surveillance project, Centers for Disease Control and Prevention. Estimates based on <20 cases or total estimates <1,200 are considered statistically unstable and are not shown (—).
[b]Implicated alone or in combination with other pharmaceuticals, alcohol, unspecified drugs, or illicit substances.
[c]Implicated alone, without other categories of pharmaceuticals, and without alcohol, unspecified drugs, or illicit substances.
[d]Annual estimates and percentages total more than 100% because a single visit may involve multiple pharmaceuticals from different categories.
[e]Annual estimates and percentages total less than 100% because additional visits involve pharmaceuticals from different categories and additional visits involve alcohol or illicit substances.
[f]Coefficient of variation >30%.
[g]*Other pharmaceuticals* includes the following: vitamin and/or mineral supplements (*n*=32 cases); hypoglycemic agents (21 cases); neurologic agents (e.g., antiparkinsonian medications) (19 cases); gastrointestinal agents (e.g., laxatives, antispasmodics [e.g., loperamide], antacids) (14 cases); genitourinary agents (e.g., erectile dysfunction medications) (13 cases); endocrine/hormone agents (12 cases); anticoagulants/antiplatelets (9 cases); antirheumatics (8 cases); antivirals (4 cases); antigout agents (3 cases); analgesic supplement (e.g., kratom) (2 cases); and unspecified prescription or over-the-counter medications (117 cases).
ED, emergency department; N/A, not applicable.

Geller et al / Am J Prev Med 2019;56(5):639–647

Source: Geller et al. 2016. DOI: 10.1016/j.amepre.2018.12.009. This is a published report on a nationally representative sample of emergency department visits for adverse effects of pharmaceutical products from 2016

Average age of initiation for various substances

Among those with a history of non-oral Rx stimulant use

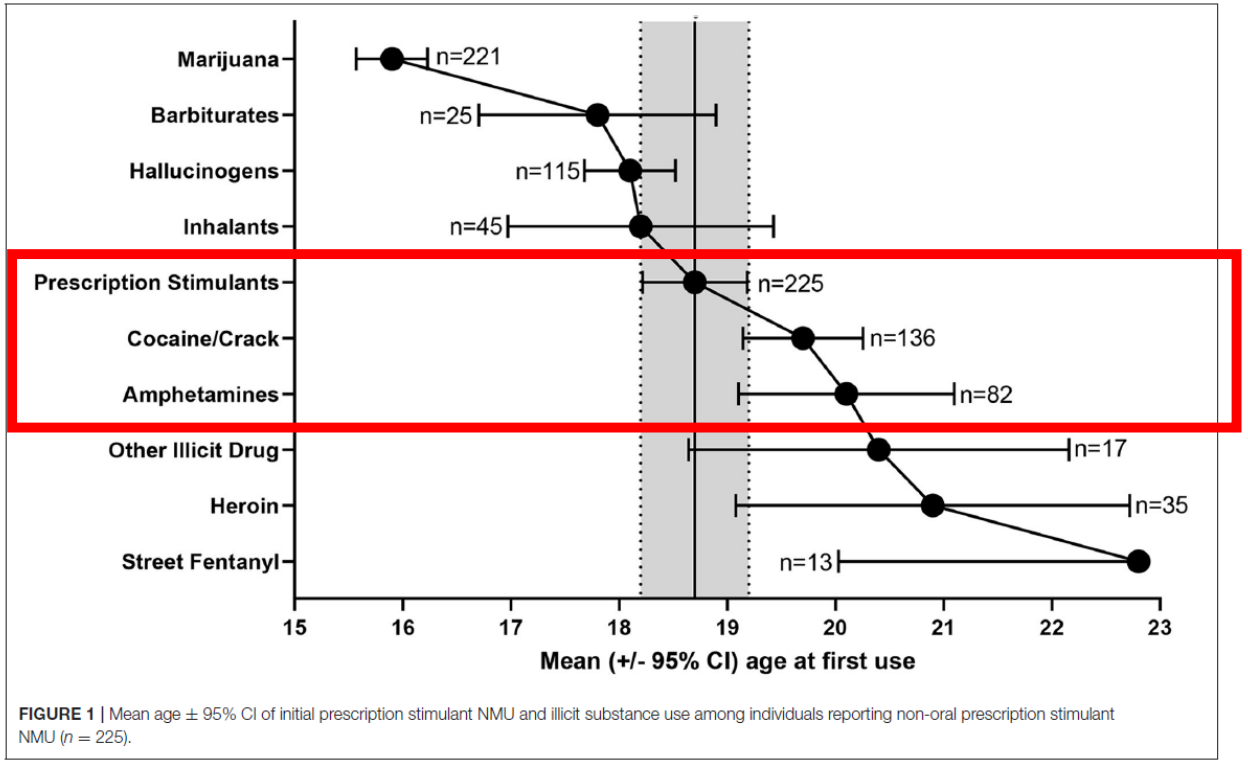
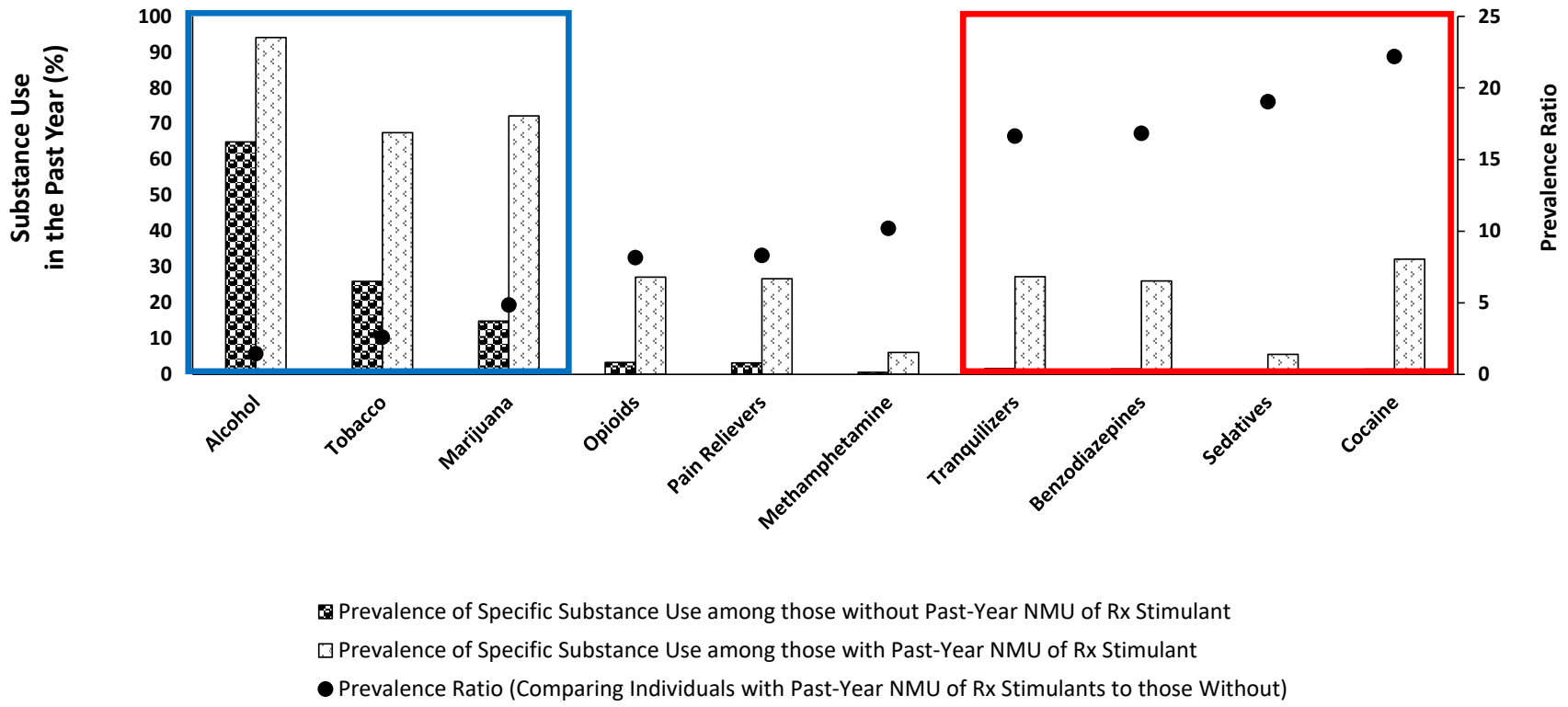


FIGURE 1 | Mean age ± 95% CI of initial prescription stimulant NMU and illicit substance use among individuals reporting non-oral prescription stimulant NMU ($n = 225$).

Source: Vosburg et al. 2021 DOI:10.3389/fpsyt.2020.631792

Polysubstance use is common among individuals with NMU of Rx stimulants, in the general population



NMU = nonmedical use
Rx = prescription

www.fda.gov

Source: FDA-generated figure from the National Survey on Drug Use and Health, 2018

Trajectory of Rx stimulant NMU

Correlates and consequences[1]

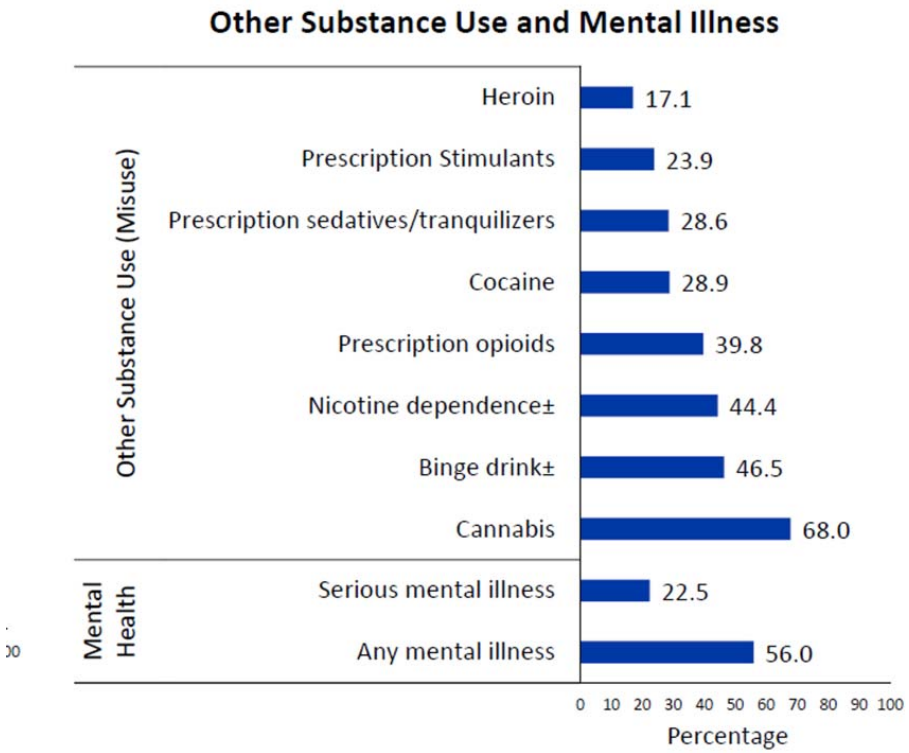
- Rx stimulant NMU and polysubstance use
- Initiation before high school graduation and problematic substance use at 35 years
- Rx stimulant NMU and neuropsychological impairment

Polysubstance use[2]

- Youth with past-year Rx stimulant NMU of any severity had higher odds of all substance use risk factors than those without NMU
  - Mild: alcohol 2.5x, marijuana 6x, cocaine 3.2x, Rx opioid/sedative 7.9x
  - Moderate/severe: alcohol 3.6x, marijuana 2.6x, cocaine 2.9x, Rx opioid/sedative 6.7x

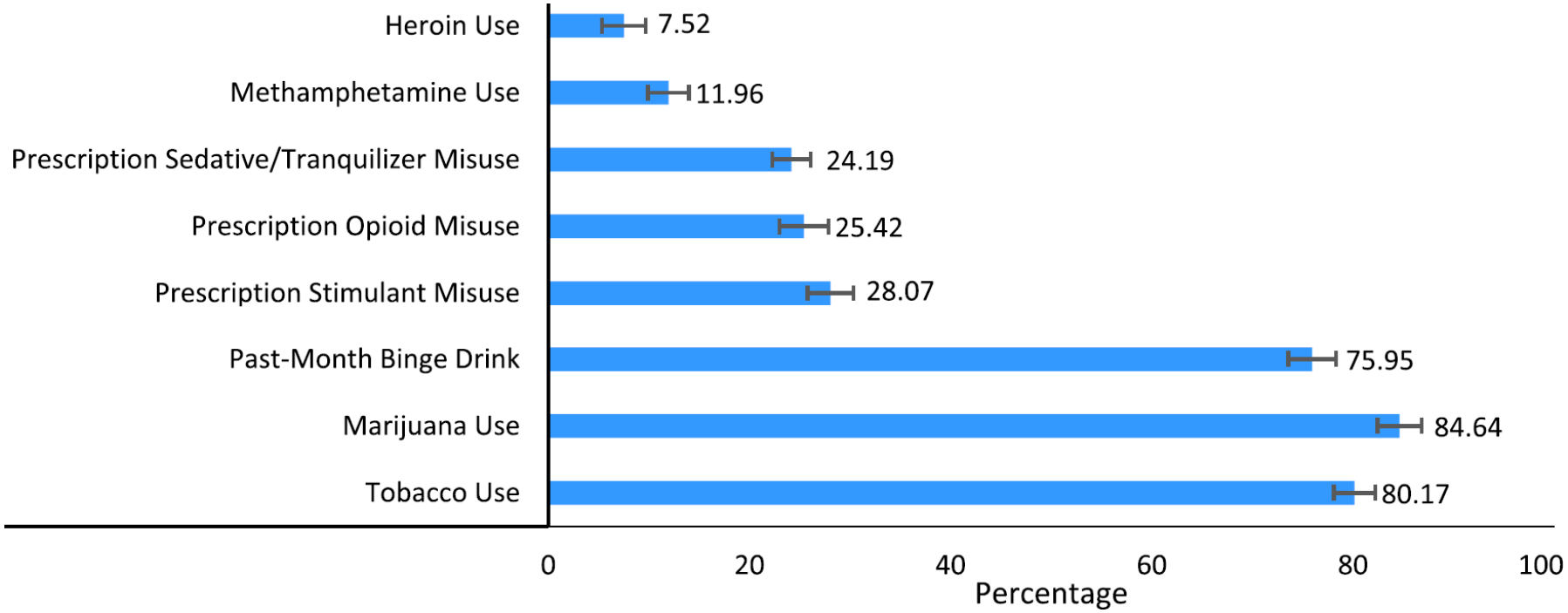
1. Schepis TS, Klare DL, Ford JA, McCabe SE. Prescription Drug Misuse: Taking a Lifespan Perspective. Subst Abuse. 2020 Mar 5;14:1178221820909352. doi: 10.1177/1178221820909352.
2. Whiteside LK, Cunningham RM, Bonar EE, Blow F, Ehrlich P, Walton MA. Nonmedical prescription stimulant use among youth in the emergency department: prevalence, severity and correlates. J Subst Abuse Treat. 2015 Jan;48(1):21-7. doi: 10.1016/j.jsat.2014.05.003. Epub 2014 Jun 10.

Methamphetamine: Use behaviors, other substance use and mental illness among past-year users, 2015-2017



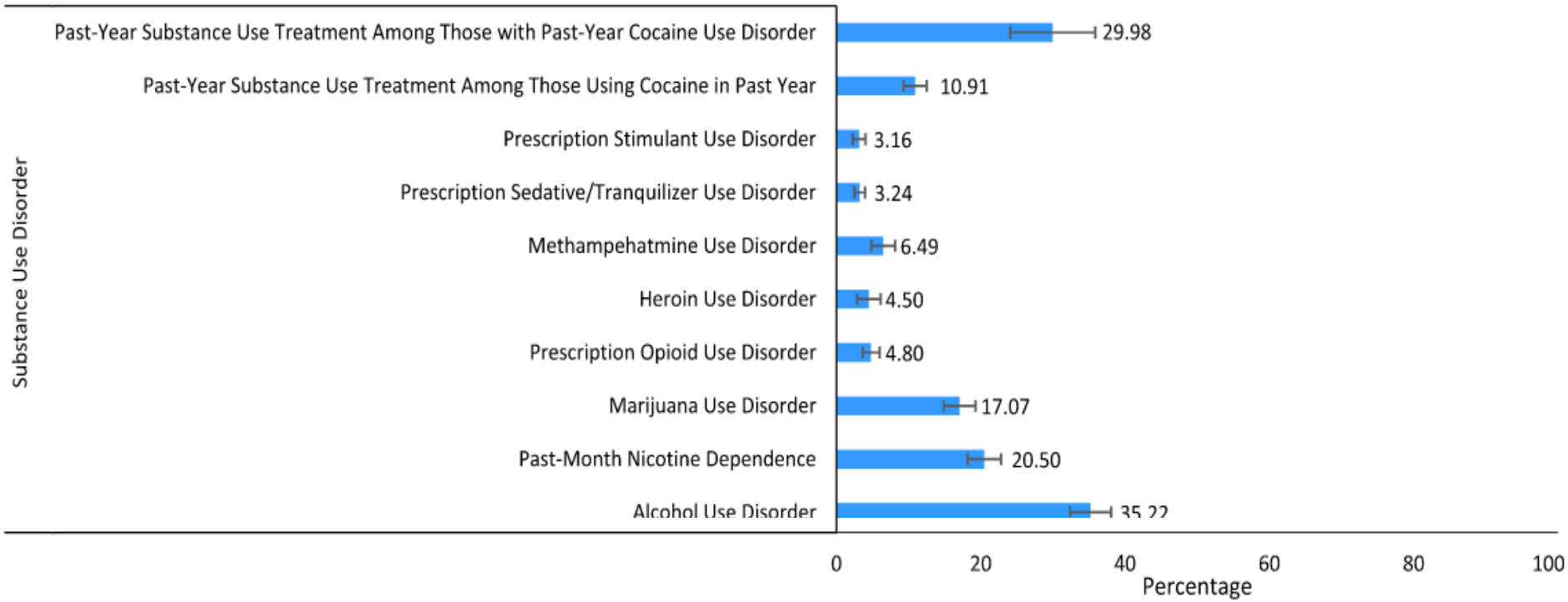
Source: Slide presented by Compton WM at the Developing Novel Therapies for Stimulant Use Disorder workshop (Dec 2019), Washington, DC. https://healthpolicy.duke.edu/events/developing-novel-therapies-stimulant-use-disorder-0; Jones CM, Mustaquim D, Compton WM. 2019

Substance use among adults reporting past-year cocaine use, 2018-2019



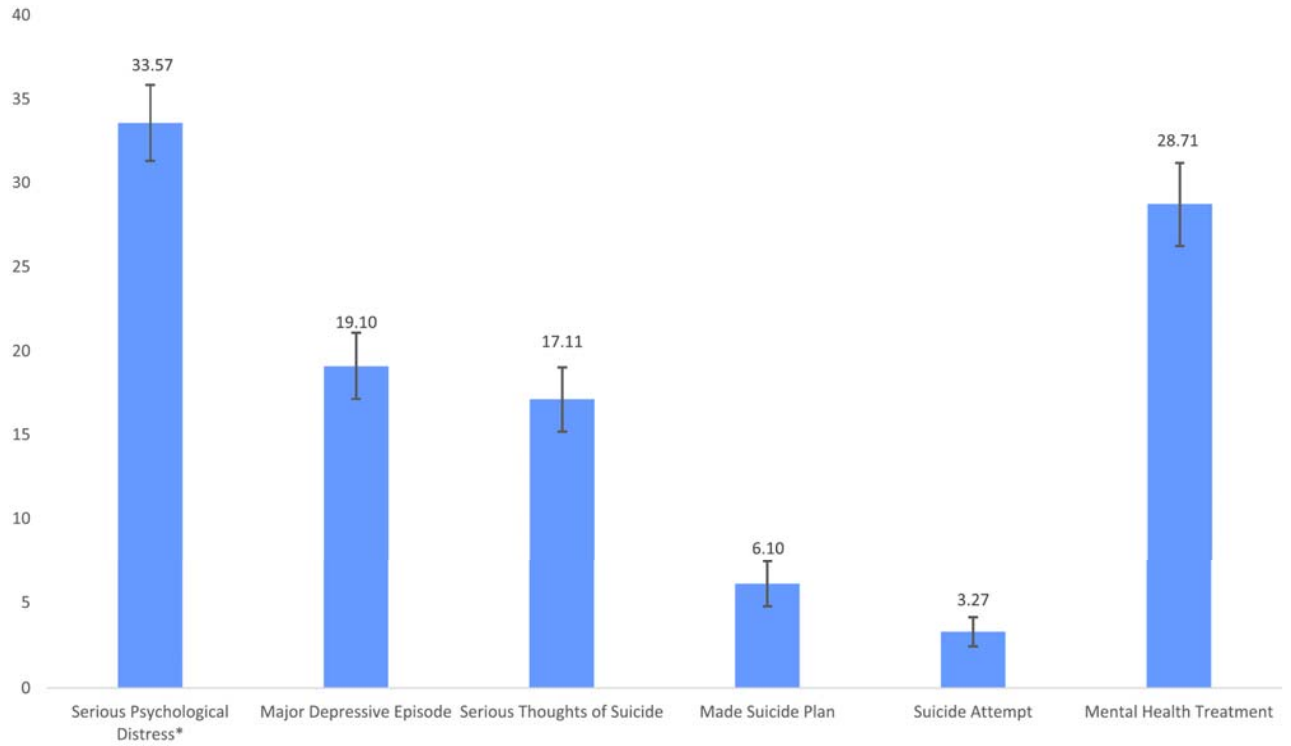
Source: Mustaquim D et al. Addict Behav. 2021 Apr 20;120:

Substance use disorders among adults reporting past-year cocaine use, 2018-2019



Source: Mustaquim D et al. Addict Behav. 2021 Apr 20;120:

Prevalence of past-year mental health characteristics among adults reporting past-year cocaine use, 2018-2019



Source: Mustaquim D et al. Addict Behav. 2021 Apr 20;120:

FDA's Integrated Approach to Accelerating Treatment Development

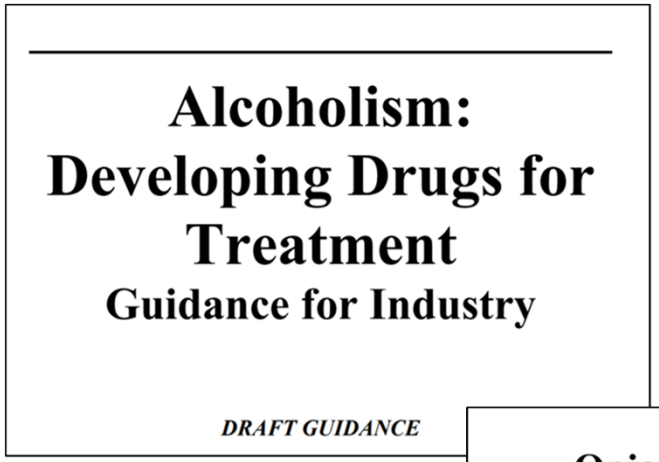
FDA-approved treatments for SUDs

Alcohol use disorder treatments

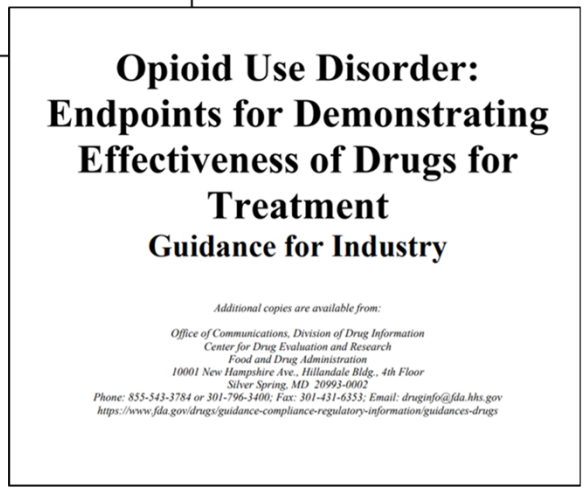
- Naltrexone
- Acamprosate
- Disulfiram

Opioid use disorder treatments

- Methadone
- Buprenorphine
- Naltrexone


Alcoholism:
Developing Drugs for Treatment
Guidance for Industry

DRAFT GUIDANCE


Opioid Use Disorder:
Endpoints for Demonstrating Effectiveness of Drugs for Treatment
Guidance for Industry

Additional copies are available from:

Office of Communications, Division of Drug Information
Center for Drug Evaluation and Research
Food and Drug Administration
10001 New Hampshire Ave., Hillandale Bldg., 4th Floor
Silver Spring, MD 20993-0002
Phone: 855-543-3784 or 301-796-3400; Fax: 301-431-6353; Email: druginfo@fda.hhs.gov
https://www.fda.gov/drugs/guidance-compliance-regulatory-information/guidances-drugs

Drug development programs for stimulant use disorder

Single Site Efficacy Trials

NS2359 vs. cocaine use disorder
(DAT/NET/SERT inhibitor)
K. Kampman; U Penn/Dana Foundation; N=80; Estimated completion date June 2021

Adderall vs. cocaine use disorder
(mixed amphetamine salts)
K. Carpenter/F. Levin; Columbia; NIDA grant R01-DA034087; N=155; Estimated completion date April 2020

Bupropion vs. cocaine use disorder
(DAT/NET inhibitor)
K. Dunn; Johns Hopkins; NIDA grant R01-DA034047; N=200; Estimated completion January 2020

Guanfacine vs. cocaine use disorder with comorbid substance use disorders – women only
(alpha2A agonist)
R. Sinha; Yale; NIDA grant R01-DA047094; N=100; Estimated completion date June 2021

Multi-Site Efficacy Trials

Lorcaserin vs. cocaine use disorder
(5-HT2C agonist)
NIDA/VACSP; 12 sites; N=272; draft clinal study report under review

Mavoglurant vs. cocaine use disorder
(mGluR5 antagonist)
Novartis; 12 sites; N=68; Estimated completion date January 2020

Ketamine vs. cocaine use disorder
(subanesthetic doses)
E. Dakwar/Columbia; NIDA grant U01-DA040646; 2 sites, N=150; Estimated completion date April 2021

EMB-001 vs. cocaine use disorder
(metyrapone/oxazepam)
B. McCarthy/Embera; NIDA grant U01-DA038879; N

Phase I

dAd5GNE (anti-cocaine vaccine)
R. Crystal; Cornell; NIDA grant U01-DA048524 - Recruiting

h2E2 (anti-cocaine mAb)
A. Norman; U Cincinnati; NIDA grant U01-DA048525 – IND approved

Cocaine hydrolase gene therapy
W.S. Brimijoin; Mayo; NIDA grant UH3-DA042492 – IND approved

Phase Ib or IIa Studies

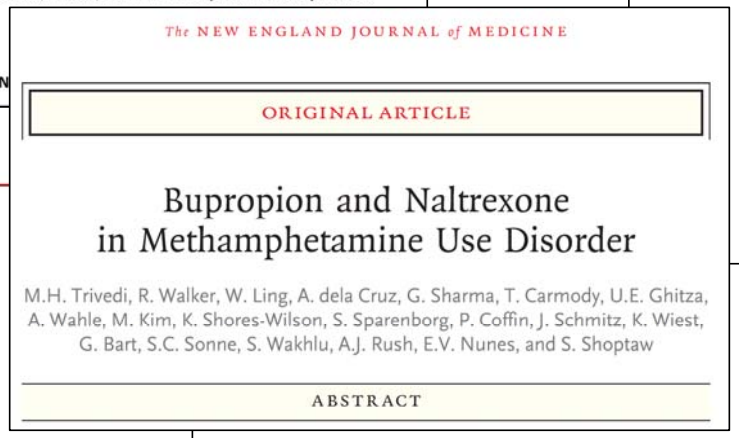
IXT-m200 – Methamphetamine users
(Anti-meth mAb) M. Stevens; Intervexion; NIDA grant U01-DA045366

Pomaglumetad methionil – Methamphetamine users
(mGluR2/3 agonist prodrug) K. Heinzerling; UCLA; NIDA grant R01-DA043238

Duloxetine & Methylphenidate – Methamphetamine users
(DAT/NET/SERT inhibition) C. Rush; U Kentucky; NIDA grant R01-DA047391

tDCS – Cocaine users
(device) A. Datta; Soterix; NIDA SBIR contract HHSN271201800035C

Cariprazine – Cocaine users
(D3/D2/5HT1A partial agonist) A.R. Childress; U Penn; NIDA grant R01-DA039215


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Bupropion and Naltrexone in Methamphetamine Use Disorder

M.H. Trivedi, R. Walker, W. Ling, A. dela Cruz, G. Sharma, T. Carmody, U.E. Ghitza, A. Wahle, M. Kim, K. Shores-Wilson, S. Sparenborg, P. Coffin, J. Schmitz, K. Wiest, G. Bart, S.C. Sonne, S. Wakhlu, A.J. Rush, E.V. Nunes, and S. Shoptaw

ABSTRACT

Presented by D. McCann at the Developing Novel Therapies for Stimulant Use Disorder meeting
https://healthpolicy.duke.edu/sites/default/files/2020-03/master_slide_deck_stimulant_use_disorder_meeting.pdf

Polysubstance use is often an exclusion criterion for clinical trials

Treatment Seeking Participants With Opioid Use Disorders Assessing Tolerability of Depot Injections of Buprenorphine

Exclusion Criteria:

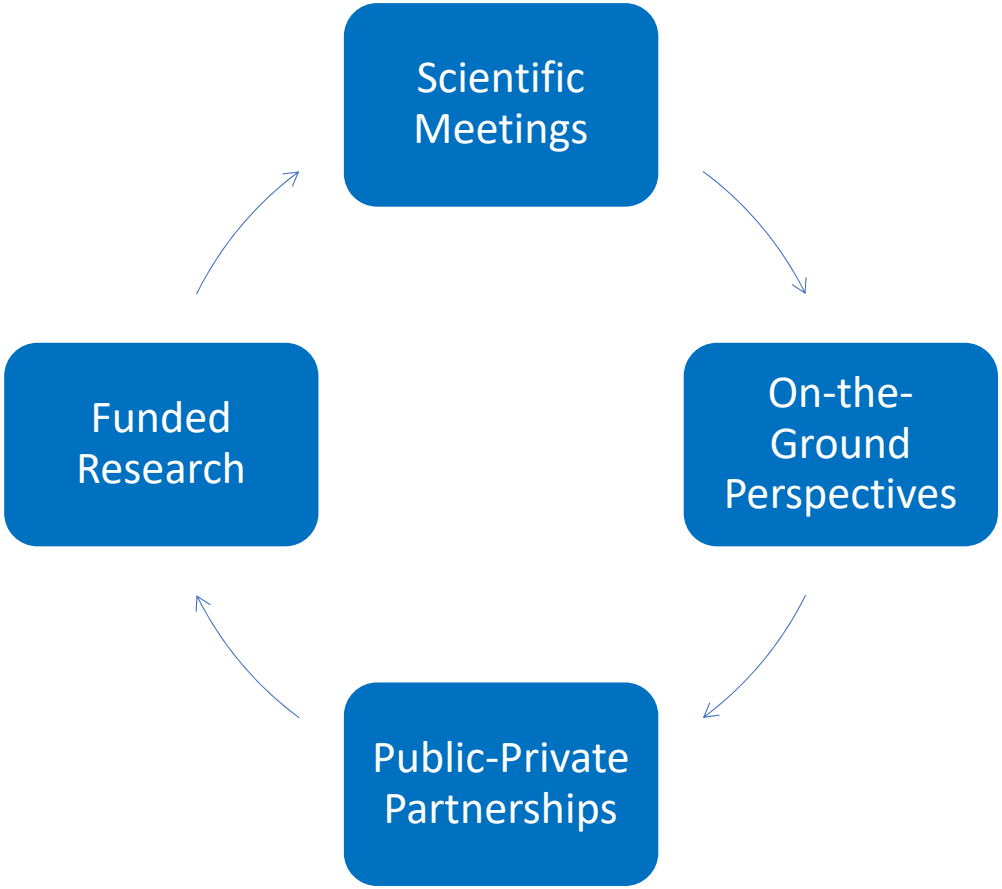
- Current diagnosis other than opioid use disorder requiring chronic opioid treatment
- Current substance use disorder as defined by DSM-5 criteria with regard to any substances other than opioids, cocaine, cannabis, tobacco, or alcohol.
- Positive urine drug screen (UDS) result at screening for cocaine or cannabis AND meets DSM-5 criteria for either moderate or severe cocaine or cannabis use disorder, respectively
- Meets DSM-5 criteria for moderate or severe alcohol use disorder
- Received medication-assisted treatment for opioid use disorder (e.g., methadone, buprenorphine) in the 90 days prior to providing written informed consent

A Phase II Trial of Varenicline for the Treatment of Cocaine Dependence

Exclusion Criteria:

1. Current DSM-IV diagnosis of any psychoactive substance dependence other than cocaine, alcohol, or nicotine dependence, as determined by the SCID.
2. Subject is, in the investigator's opinion, at risk of requiring medical detoxification for alcohol dependence during the study.
3. Concomitant treatment with psychotropic medications.
4. Current gambling problems. This will be assessed by the patient's self-report.

Activities to accelerate development of substance use disorder treatments



Scientific meetings

FDA-led meetings

- Workshop: Developing Novel Therapies for Stimulant Use Disorder
- Organized in collaboration with Duke-Margolis

https://healthpolicy.duke.edu/events/developing-novel-therapies-stimulant-use-disorder-0

NIDA-led meetings

- Workshop #1: Target identification for methamphetamine use disorder treatment
- Workshop #2: Opioid and methamphetamine interactions

Non-federal meetings

- Measures of Outcomes for Stimulant Trials (MOST) Meeting
  - Discussed ideas, research agenda on potential endpoints for PSUD
- RADARS System Scientific Meetings
- Many others

On-the-ground perspectives

Patient-Focused Drug Development meetings - Stimulant Use Disorder	Network of Experts calls with clinicians
• Patients' perspectives on health effects and daily impacts, lived experience and therapies, treatment goals, experiences with polysubstance use	• Clinicians' experiences of and thoughts on barriers and facilitators to providing care, behavioral treatment, costs of treatment, prescription stimulants' role in PSUD, etc.

On-the-ground perspectives: Polysubstance use

"Because cocaine, like other stimulants such as methamphetamine, has a very harsh come down and very strong cravings … I began to add heroin into my cocaine injections. Of course I then became opiate dependent … As we as a country demonized heroin and opiates, I have seen many of my patients in clinic who are addicted to heroin or opiates switch to readily available methamphetamine, which certainly provided the dopamine spike that their brains were looking for. " – *Panelist from PFDD meeting on PSUD*

"I started using drugs at age 13. I was genetically predisposed to addiction on both sides of my family … I started using opioids as a way to come down off cocaine, when I was in college." – *Panelist from PFDD meeting on OUD*

On-the-ground perspectives: Polysubstance use

"We've found within our patient community that three out of four are struggling with polysubstance use. Individuals just don't typically struggle with one particular drug over the other. It ends up being a polysubstance use disorder." – *Panelist from PFDD meeting on PSUD*

"I have a large proportion of my patients who are people who are experiencing homelessness … So I see a ton of people who didn't use stimulants before who started using meth really just to stay awake and to help them with vigilance so that they could protect themselves, so that they wouldn't be assaulted, and so that their things wouldn't be stolen … Particularly, some people do that with just methamphetamines, but we also have a fair number of folks who use opioids and then use methamphetamines to help them not nod out, to stay awake, and to stay vigilant." – *Participant in Network of Experts call on PSUD*

Public-private partnerships: Reagan-Udall Foundation projects

Maps of patient journeys

- Create visual analyses of patients' trajectory of use
- Inform consideration of approaches to SUD prevention and Tx

Stakeholder event with payors

- Convened meeting on payors' perspectives on SUD Tx
- Understand RWE landscape surrounding SUD Tx development and uptake

Real-World Evidence Accelerator

- Used COVID-19 Evidence Accelerator framework
- Exploratory focus on if/how real-world data can complement RCT framework for PSUD Tx

Funded research: Recent solicitations

FY20 External Research

- Funded epidemiological study examining stimulant abuse in the United States

FY21 External Research

- Solicited proposals to develop methods and carry out studies to better understand the trajectory of PSUD

Summary

- FDA recognizes that polysubstance use is common, given epidemiological data
- FDA continues to pursue better understanding of polysubstance use through array of stakeholder engagement and research activities

Acknowledgments

- FDA Center for Drug Evaluation and Research, Office of the Center Director, Controlled Substances Program
  - Caroline Huang, Menglu Yuan
- FDA Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology
  - Christina Greene, Jana McAninch, Rose Radin, Amy Seitz, Joe Shearer, Judy Staffa
- FDA Center for Drug Evaluation and Research, Office of New Drugs, Office of Neuroscience, Division of Anesthesiology, Addiction Medicine, and Pain Medicine
  - Celia Winchell