



Stimulant Use and Nonmedical Use

Joseph Shearer, PhD, MPH

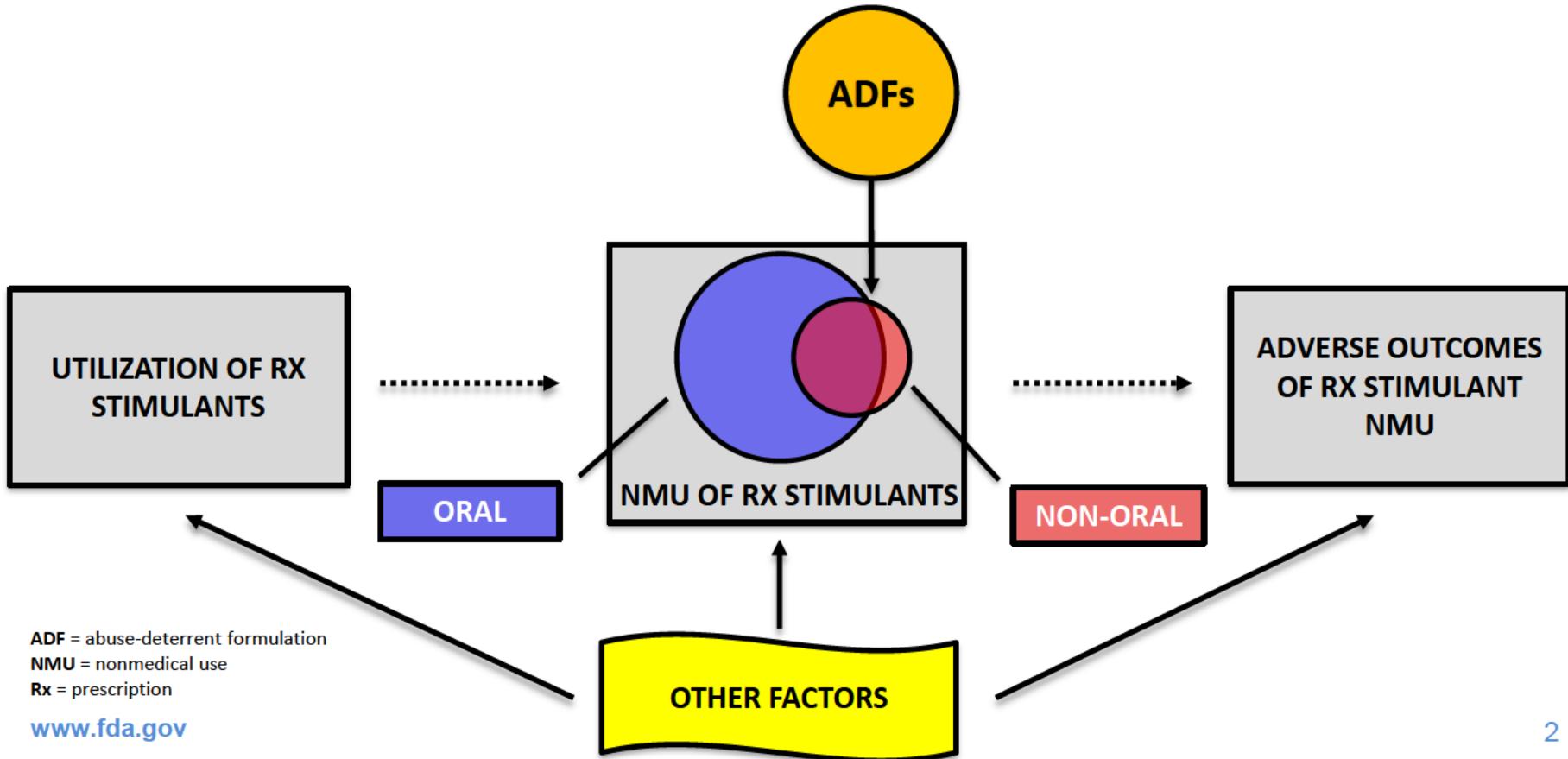
Division of Epidemiology II

Office of Surveillance and Epidemiology

Center for Drug Evaluation and Research

NDA 211179: Joint PDAC & DSaRM Advisory Committee Meeting
October 8, 2020

Considering Potential Public Health Impact of ADF Rx Stimulants



Differential Impacts Possible for Specific Populations (1)*



People not currently using Rx stimulants nonmedically, including patients and others

Individuals who use Rx stimulants nonmedically, but not regularly through non-oral routes

Individuals who NMU Rx stimulants, regularly through non-oral routes

Desired impacts

- Reduce risk of initiating non-oral NMU
- Reduce risk of associated harms

Potential unintended impacts

- Adverse effects from added excipients
- Misperceptions about safety benefits of ADF stimulants

Differential Impacts Possible for Specific Populations (2)*



People not currently using Rx stimulants nonmedically, including patients and others

Desired impacts

- Reduce risk of initiating non-oral NMU
- Reduce risk of associated harms

Potential unintended impacts

- Adverse effects from added excipients
- Misperceptions about safety benefits of ADF stimulants

Individuals who use Rx stimulants nonmedically, but not regularly through non-oral routes

Desired impacts

- Reduce risk of transitioning to regular non-oral NMU
- Reduce harms associated with non-oral NMU

Potential unintended impacts

- Hastening transition to more harmful substances
- Adverse effects from defeating ADF properties

Individuals who NMU Rx stimulants, regularly through non-oral routes

Differential Impacts Possible for Specific Populations (3)*



People not currently using Rx stimulants nonmedically, including patients and others

Desired impacts

- Reduce risk of initiating non-oral NMU
- Reduce risk of associated harms

Potential unintended impacts

- Adverse effects from added excipients
- Misperceptions about safety benefits of ADF stimulants

Individuals who use Rx stimulants nonmedically, but not regularly through non-oral routes

Desired impacts

- Reduce risk of transitioning to regular non-oral use
- Reduce harms associated with non-oral use

Potential unintended impacts

- Hastening transitioning to more harmful substances
- Adverse effects from defeating ADF properties

Individuals who use Rx stimulants, regularly through non-oral routes

Desired impacts

- Reduce non-oral use
- Reduce harms associated with non-oral use

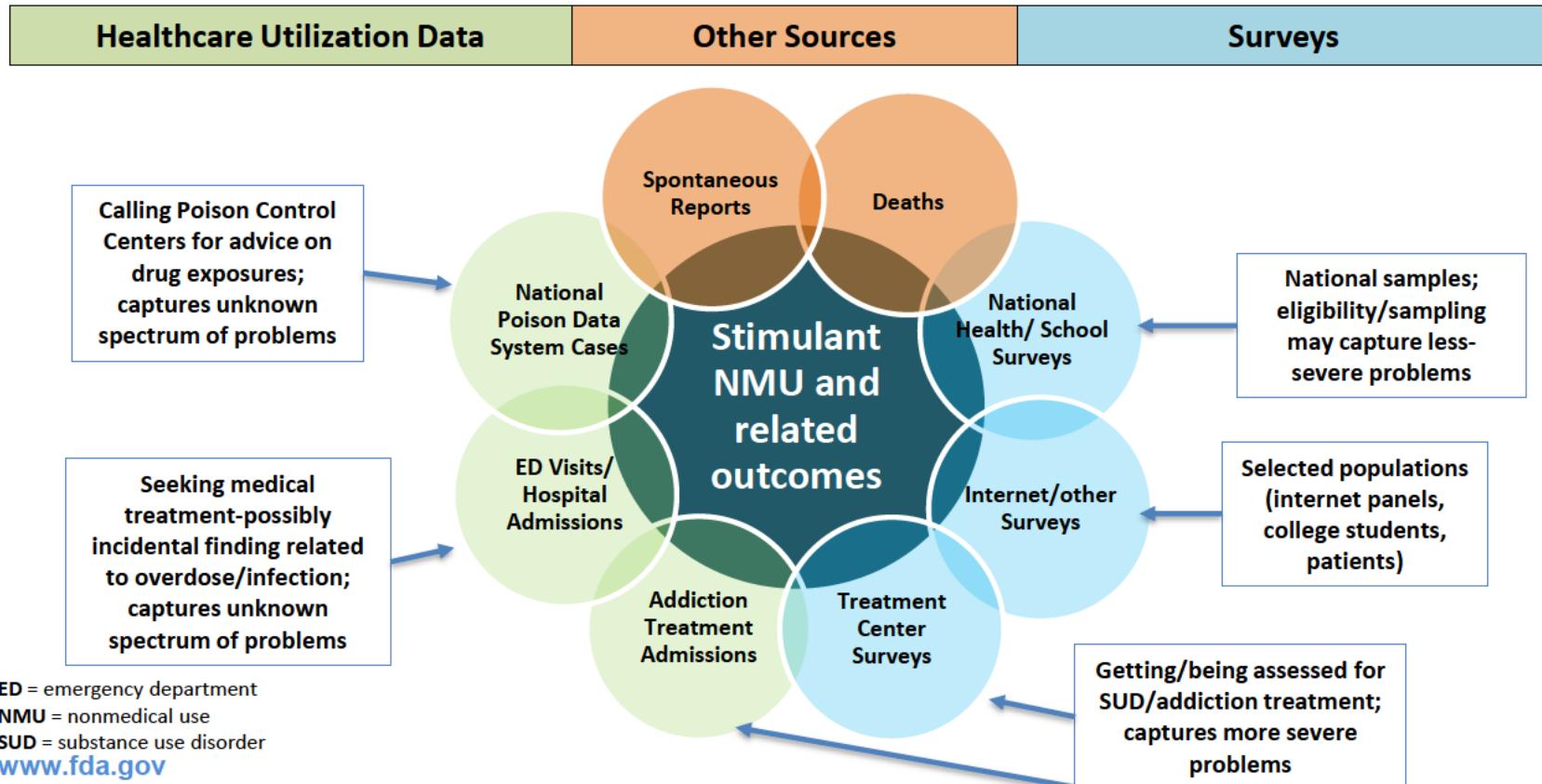
Potential unintended impacts

- Substituting more harmful substances
- Adverse effects from defeating ADF properties

Comparing Stimulants to Opioid Analgesics

- Opioid analgesics are the only other drug class with labeled ADFs
 - AR19 Applicant followed the 2015 Guidance for Abuse-Deterrent Opioids—Evaluation and Labeling¹
- Will provide data on utilization, nonmedical use, and harms associated with prescription opioids
- Use ADF opioid analgesic experience to inform discussion about the potential public health impact of ADF stimulants
 - **Noting that patterns of use, nonmedical use (NMU), and harms differ for opioids and stimulants**

No Single Data Source Provides the Whole Picture



Sources of Information

- **Applicant Documents**

- Multiple Module Information: Prescription stimulant NMU data and AR19 manipulation resistant and NMU deterrent data
- Several epidemiologic study reports prepared for the Applicant that provided information on use and NMU patterns, including route of administration, among the general population, college students, adolescents, and those with a history of non-oral use
- Pinney Associates report on the public health rationale for AR19

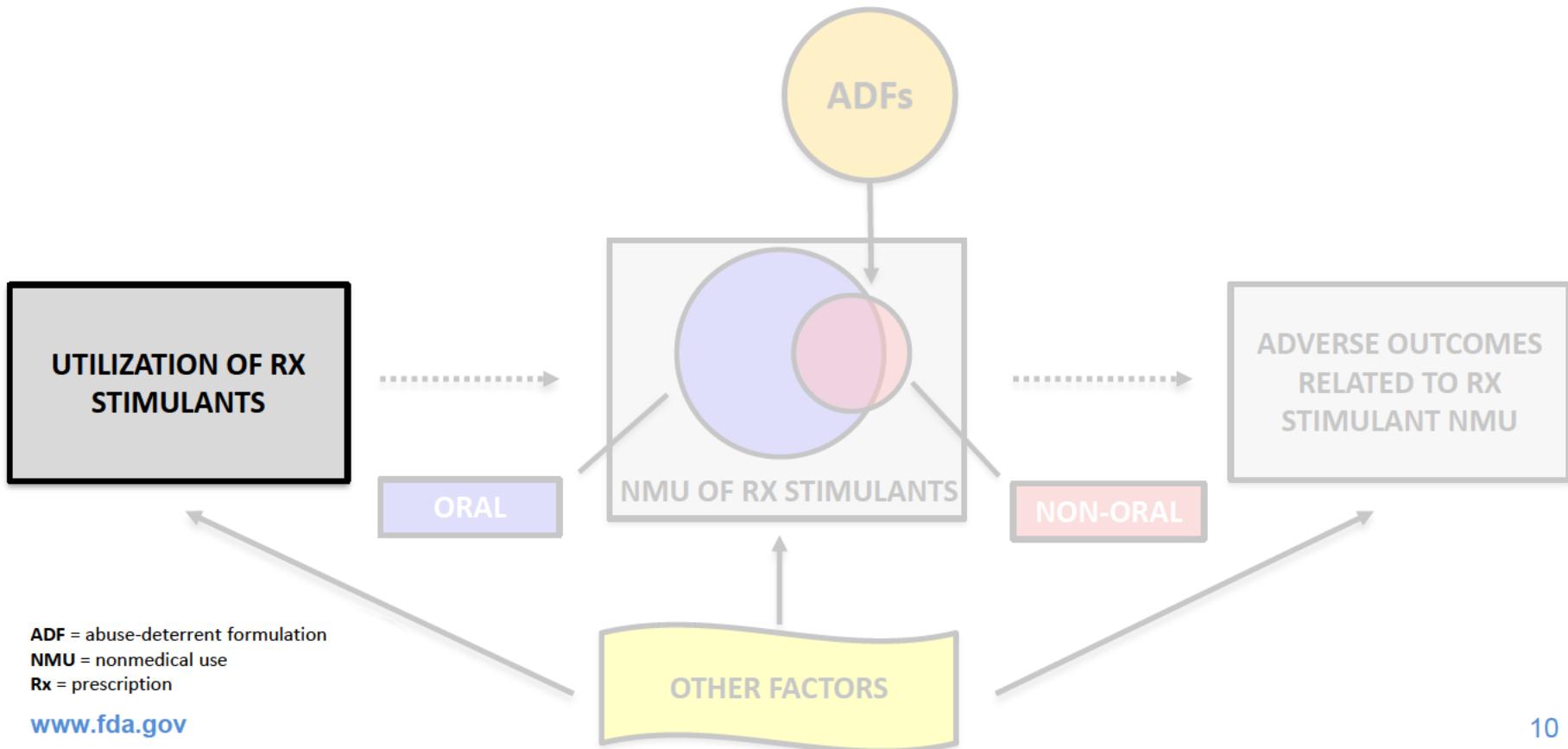
- **FDA Analyses**

- Adverse event reports (FAERS)
- Prescription outpatient retail dispensing data (IQVIA NPA®, IQVIA TPT™, SH)
- Diagnoses associated with CII stimulant prescriptions (Syneos Treatment Answers)
- General population surveys (NSDUH, MTF)
- People seeking medical advice or care (NPDS - poison control center cases, NEISS-CADES - emergency department visits)
- People seeking treatment (TEDS, ASI-MV®)
- Overdose deaths (NVSS-M, DIM)
- Review of relevant case reports and case series

Defining Nonmedical Use (NMU)

- **Misuse:** the intentional therapeutic use of a drug product in an inappropriate way and specifically excludes the definition of abuse¹
- **Abuse:** the intentional, non-therapeutic use of a drug product or substance, even once, to achieve a desirable psychological or physiological effect¹
- **NMU:** either misuse or abuse

Considering Potential Public Health Impact of ADF Rx Stimulants



Overview of the CII Stimulant Prescription Market*

- Rx stimulant ADHD medication prescribing is widespread and increasing
 - Largest growth among adults ages 20 to 64 years
 - Racemic amphetamine (such as AR19) is 0.3% of stimulant market
 - In 2019, number of CII stimulant Rx roughly half that of CII opioid analgesics
- IR≈ER (unlike opioid analgesics where ~90% IR)
 - ER amphetamines more common for adolescents, IR more common for adults

ADHD = attention deficit

hyperactivity disorder

CII = Schedule II

ER = extended-release

IR = immediate-release

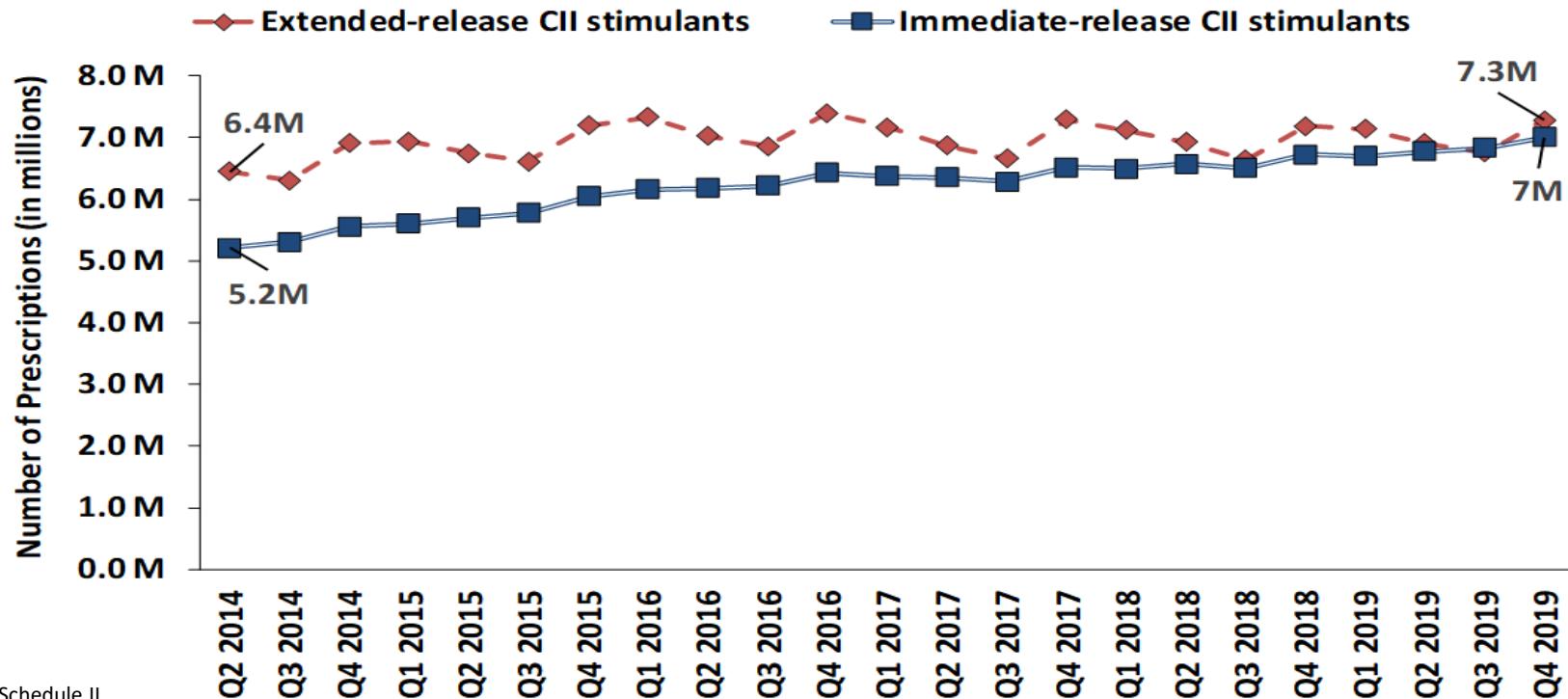
www.fda.gov

*CII drugs are defined by the Drug Enforcement Administration as having high potential for abuse, with use potentially leading to severe psychological or physical dependence (<https://www.dea.gov/drug-scheduling>). In this section, CII stimulants mean prescription stimulants indicated for ADHD, and CII opioid analgesics excludes schedule CIII-IV opioid analgesics like codeine and tramadol. Further details can be found in our briefing document, available at: <https://www.fda.gov/advisory-committees/advisory-committee-calendar/october-8-2020-joint-meeting-psychopharmacologic-drugs-advisory-committee-and-drug-safety-and-risk#event-information>.



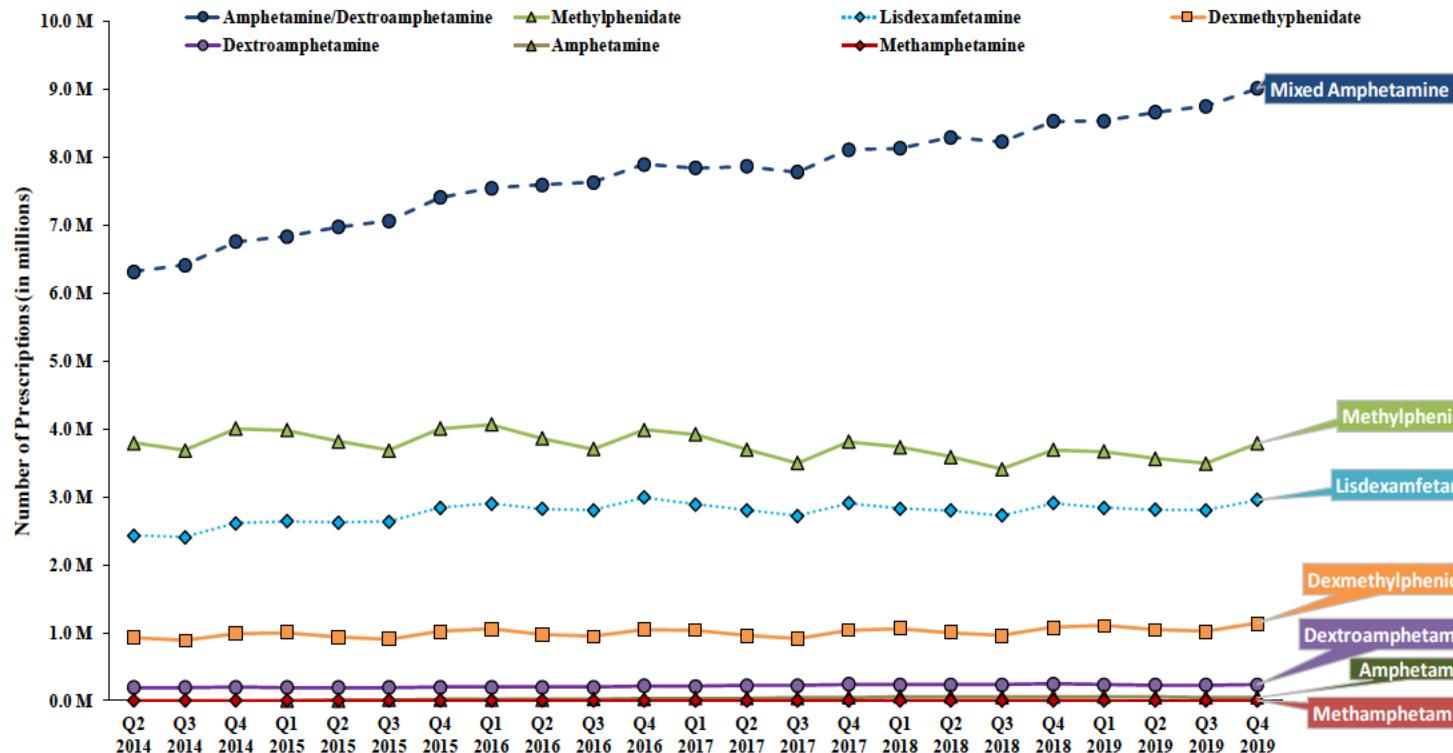
UTILIZATION OF CII STIMULANTS

Extended- and Immediate-Release CII Rx Stimulants Dispensed Were Similar in 2019



CII = Schedule II

Use of Mixed Amphetamine Salts Increased, While Racemic Amphetamine Use Remained Low

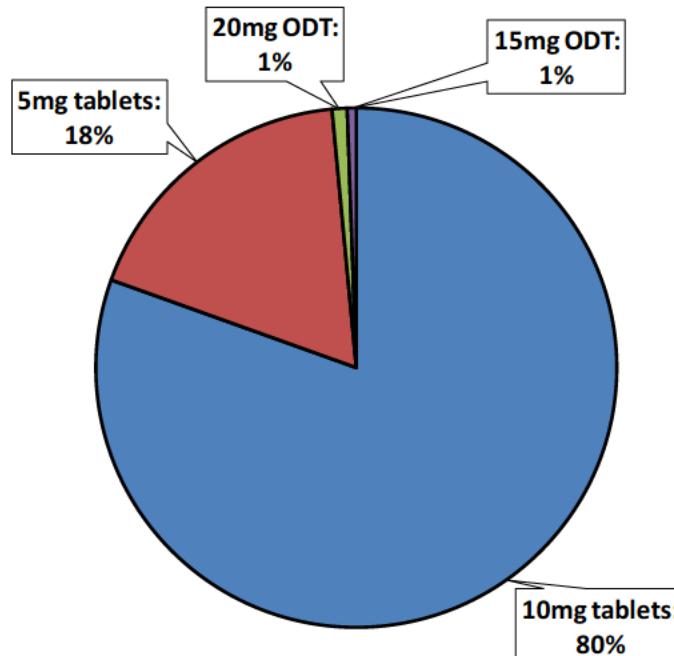


Proposed IR ADF Stimulant Product (AR19)

10mg and 5mg Were Top Strengths Dispensed for IR Racemic Amphetamine Sulfate Tablets



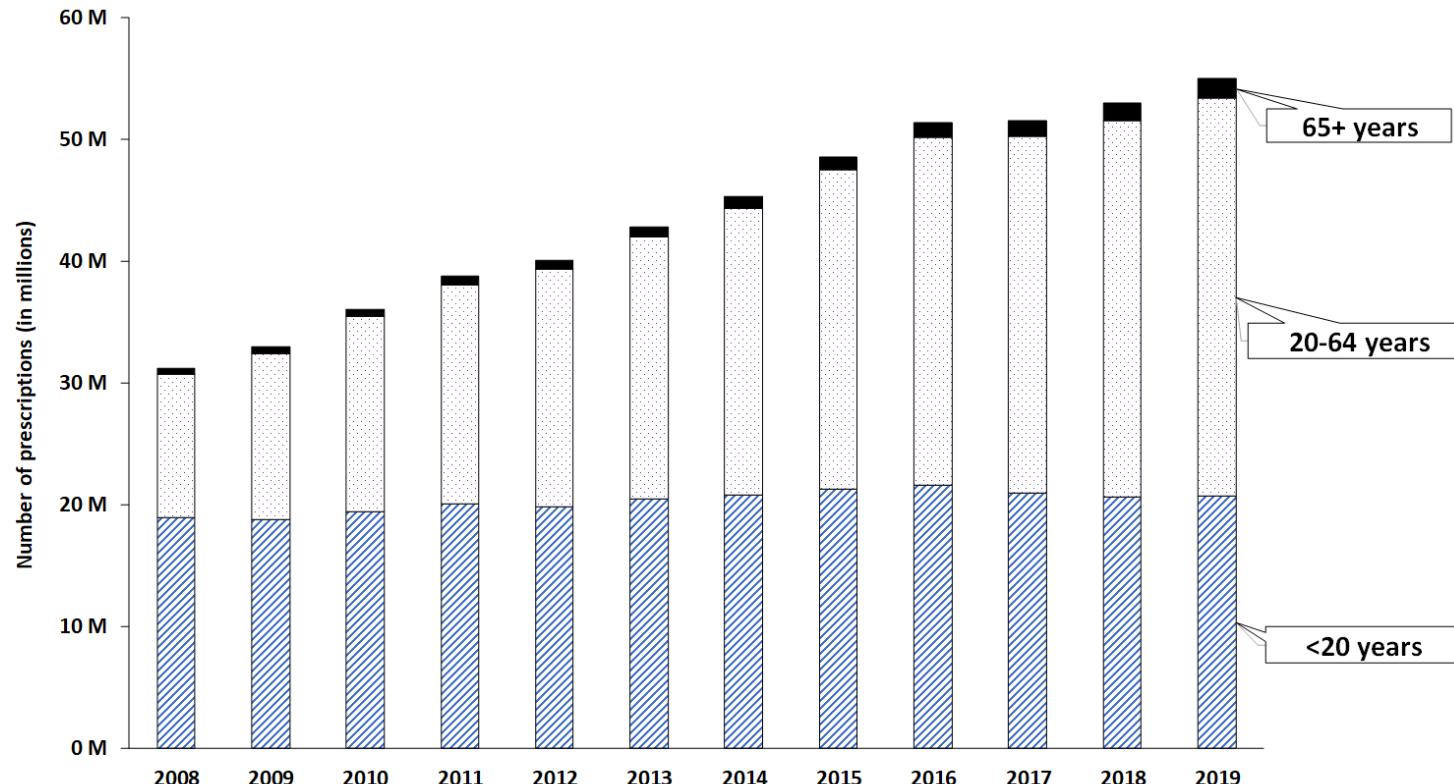
Proportion of Amphetamine Sulfate Strengths Dispensed in 2019



ODT = orally disintegrating tablet
IR = immediate-release

UTILIZATION OF CII STIMULANTS BY AGE

CII Stimulant Use Increased in Adults



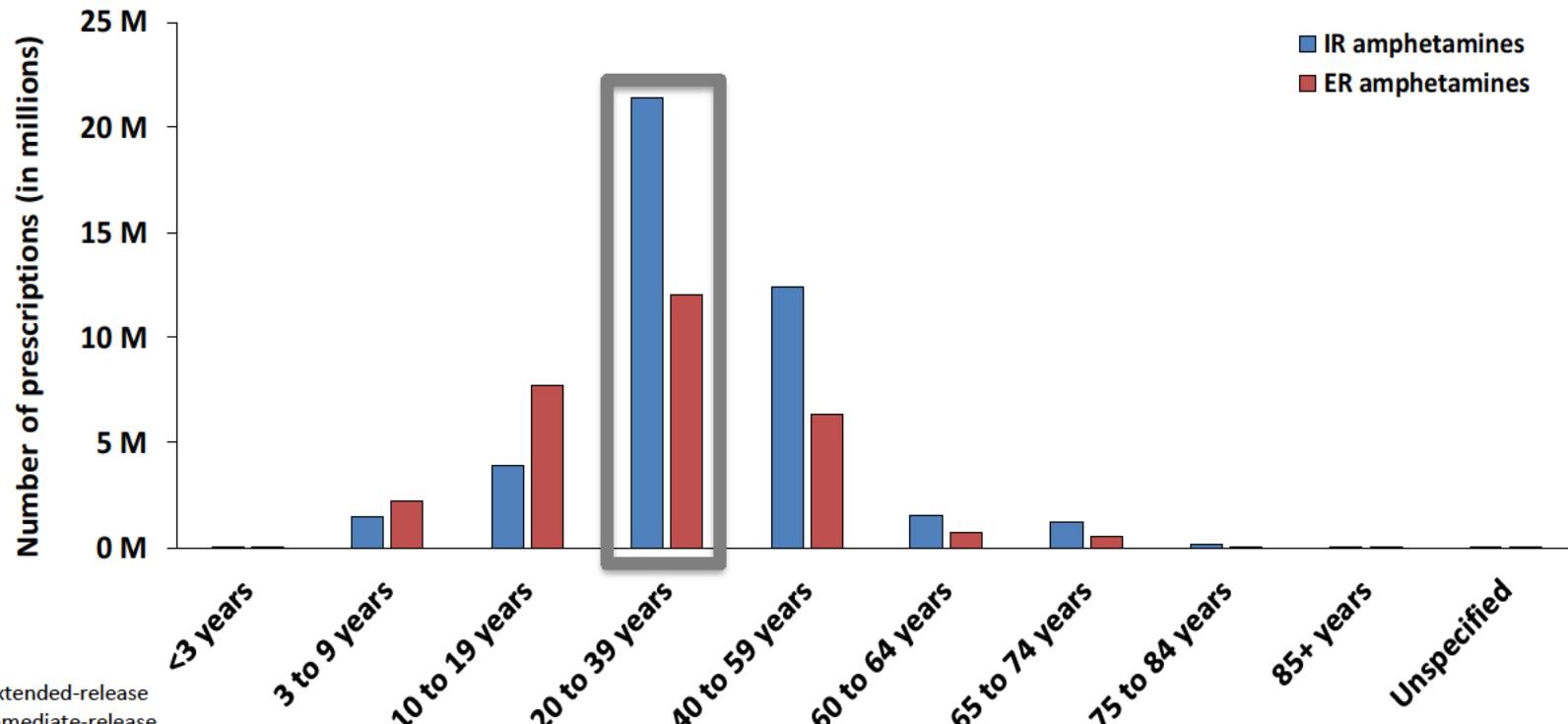
CII = Schedule II

www.fda.gov

Source: FDA analysis of National Prescription Audit Patient Insights™. 2008-2019. Extracted April 2020

17

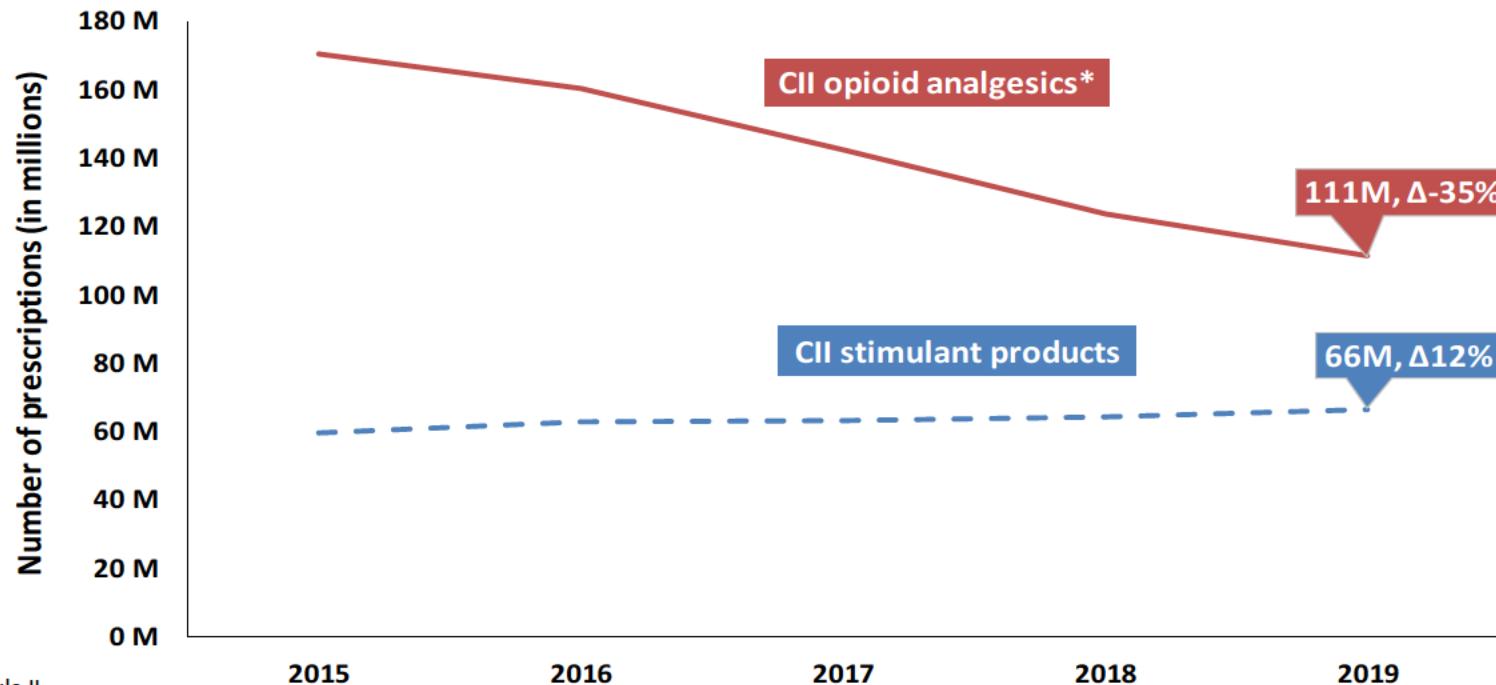
IR Amphetamine Use Higher Among Those \geq 20 years, ER Amphetamine Use Higher Among Those \leq 19 years



ER = extended-release
IR = immediate-release

UTILIZATION OF CII STIMULANTS COMPARED TO OPIOID ANALGESICS

Prescriptions for CII Opioid Analgesics Decreased, While CII Stimulant Products Increased



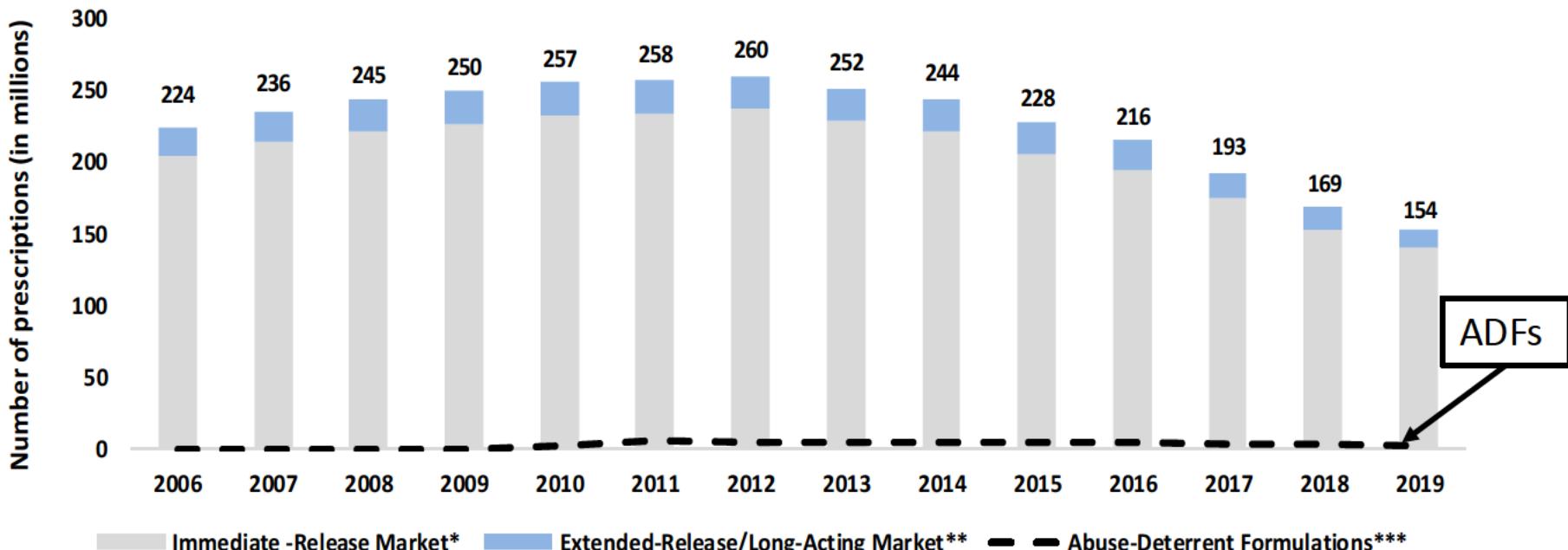
CII = Schedule II

* CII opioid analgesics include fentanyl, hydrocodone, hydrocodone-ibuprofen, oxycodone-ibuprofen, morphine-naltrexone, pentazocine-naloxone, hydromorphone, methadone, morphine, oxycodone, oxymorphone, pentazocine, tapentadol, levorphanol

www.fda.gov

Source: FDA analysis of IQVIA, National Prescription Audit™. 2019. Extracted July 2020 20

ER/LA and ADF Opioid Analgesics Represent a Small Proportion of the Opioid Analgesic Market



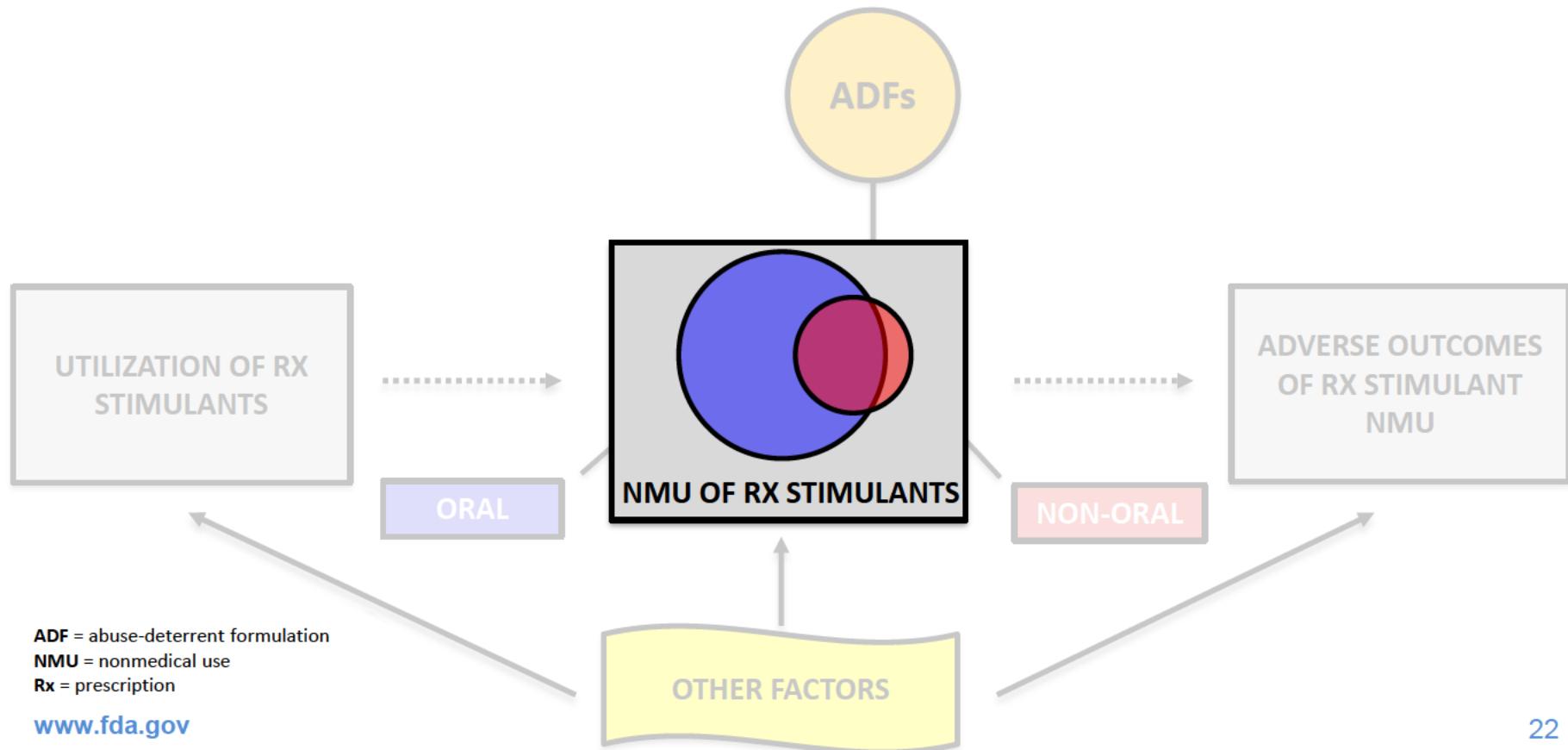
ADF = abuse-deterrent formulation; ER = extended-release; IR = immediate-release

* Immediate-Release includes oral solids, oral liquids, rectal, nasal, and transmucosal formulations

** Extended-Release/Long-Acting (ER/LA) includes oral solids and transdermal patches

*** Abuse-Deterrent Formulations (ADFs) include Arymo ER, Embeda ER, Hysingla ER, Morphabond ER, Xtampza ER, OxyContin ER Reformulated, RoxyBond IR

Considering Potential Public Health Impact of ADF Rx Stimulants



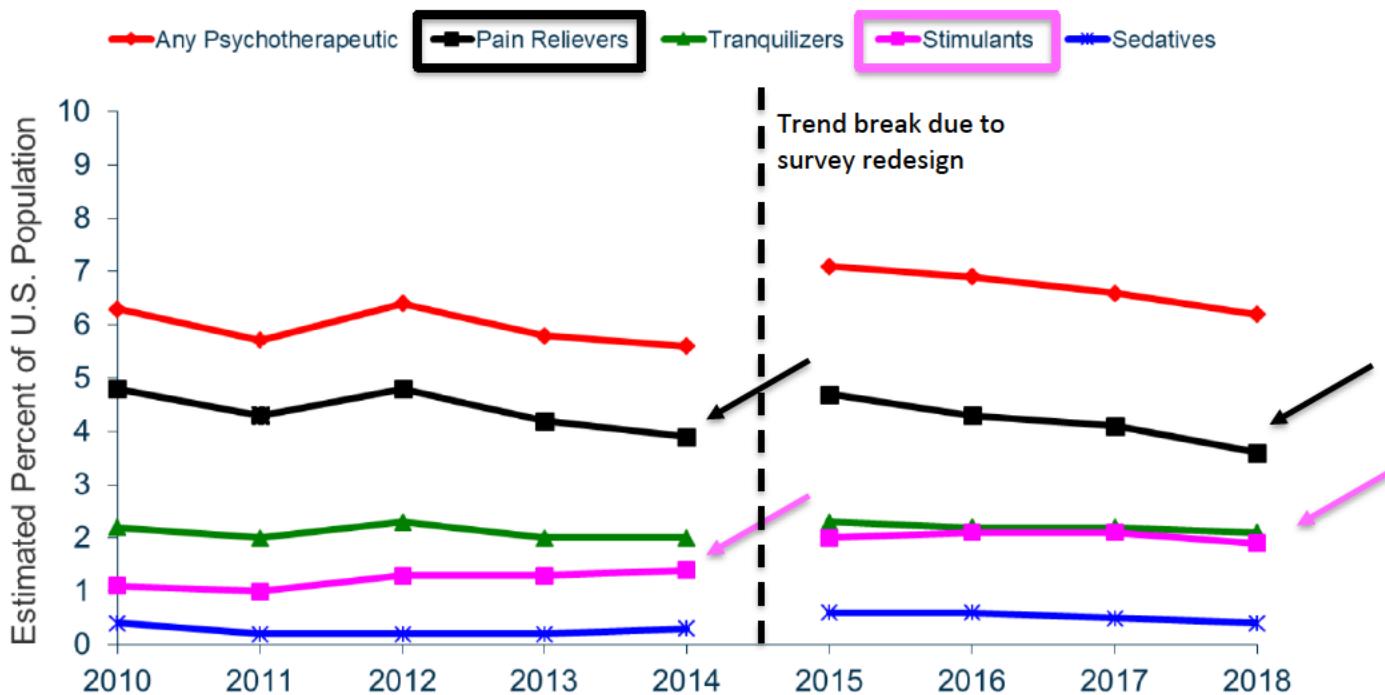
Overview of Scope and Patterns of Rx Stimulant NMU in General Population



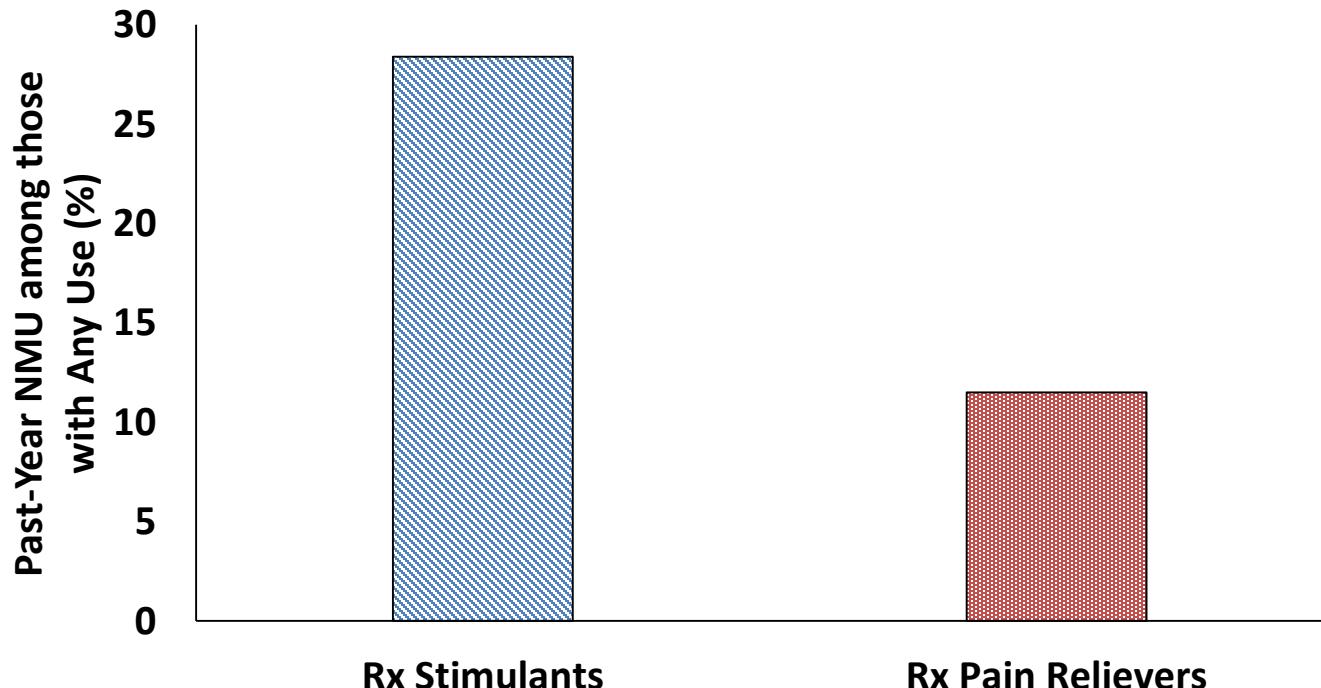
- **~5 million people in U.S. general population used Rx stimulants nonmedically in 2018**
- **Highest prevalence of NMU among young adults**
 - Particularly those in college and in fraternities/sororities
- **NMU of Rx stimulants appears relatively stable from 2010 through 2018**
- **NMU of Rx stimulants (2.0%) < NMU of opioid analgesics (3.6%)**
 - However, the % who report NMU among those who report using the drug is higher for Rx stimulants than opioid analgesics

NMU OF RX STIMULANTS - GENERAL POPULATION

NMU of Rx Stimulants has Remained Relatively Constant, While NMU of Prescription Pain Relievers has Decreased



NMU Among Individuals With Any Use is Greater for Rx Stimulants than Rx Pain Relievers



NMU = nonmedical use
Rx = prescription

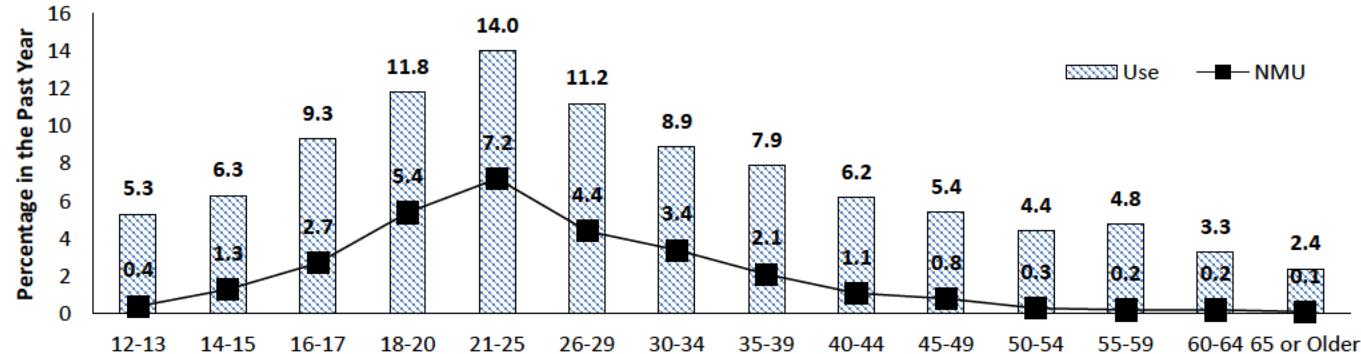
www.fda.gov

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

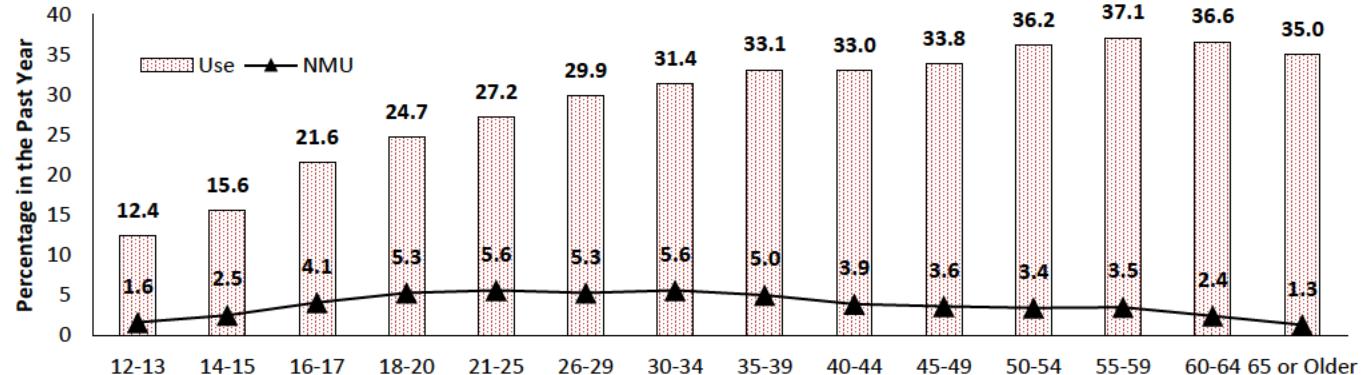
26

NMU of Rx Stimulants Peaks in Young Adulthood

Rx Stimulants



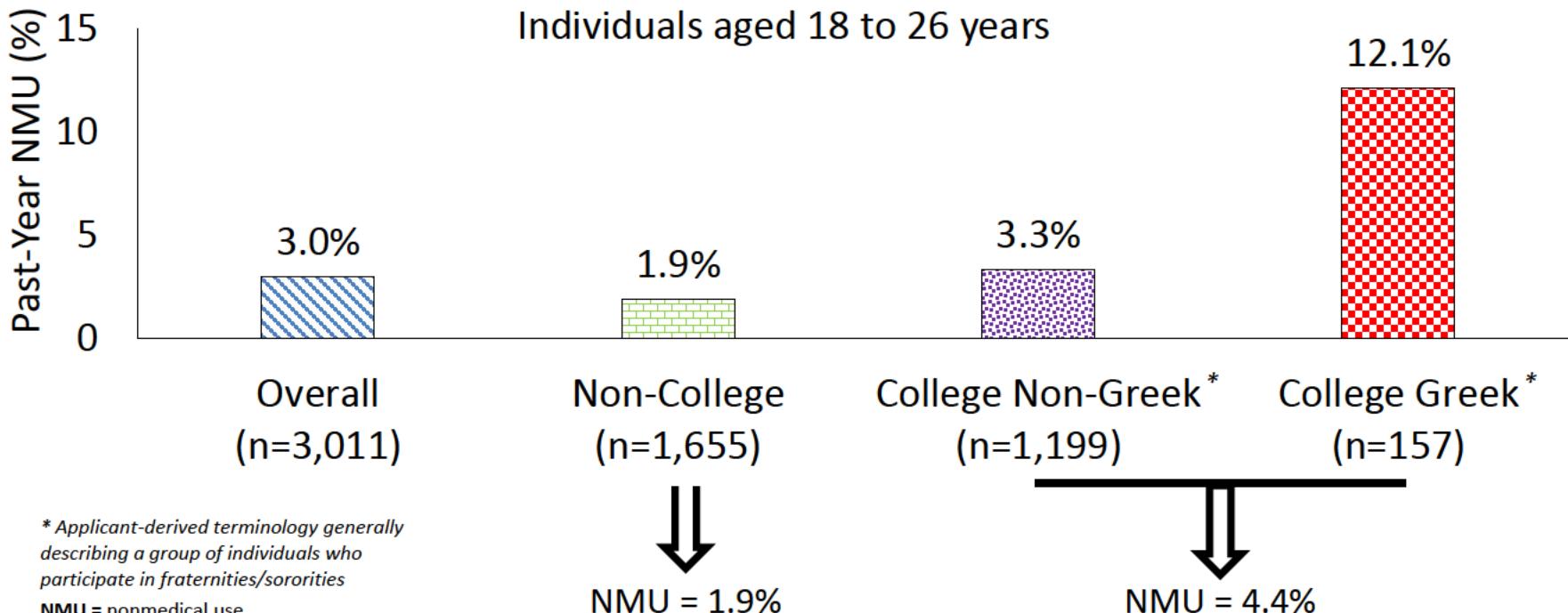
Rx Pain Relievers



NMU = nonmedical use
Rx = prescription

NMU OF RX STIMULANTS – POPULATION SUBGROUPS

NMU of Rx Stimulants is Higher Among College Students and Highest among those Participating in Fraternities or Sororities

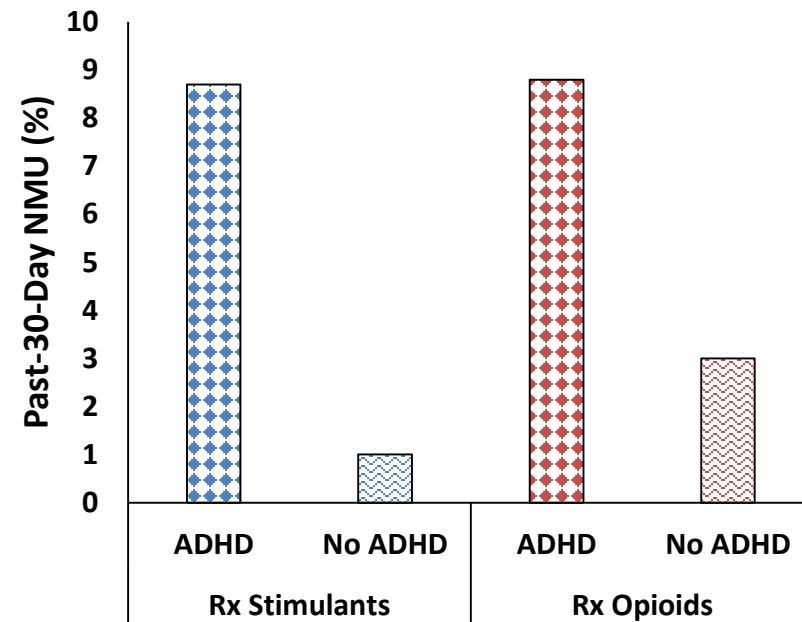


Source: FDA-generated figure. Nonmedical Use of Prescription Medications in College Students Involved in Greek Life (AR19.MA012), an Applicant-submitted online survey of the general U.S. population aged 18 to 26 years conducted by the internet panel company YouGov

NMU of Rx Stimulants and Rx Opioids More Common in Individuals with ADHD



- NMU of Rx stimulants and opioids was greater among those with ADHD
- Psychiatric comorbidities were more common among individuals with use of Rx stimulants nonmedically
 - e.g., ADHD, depression, anxiety



ADHD = attention deficit hyperactivity disorder

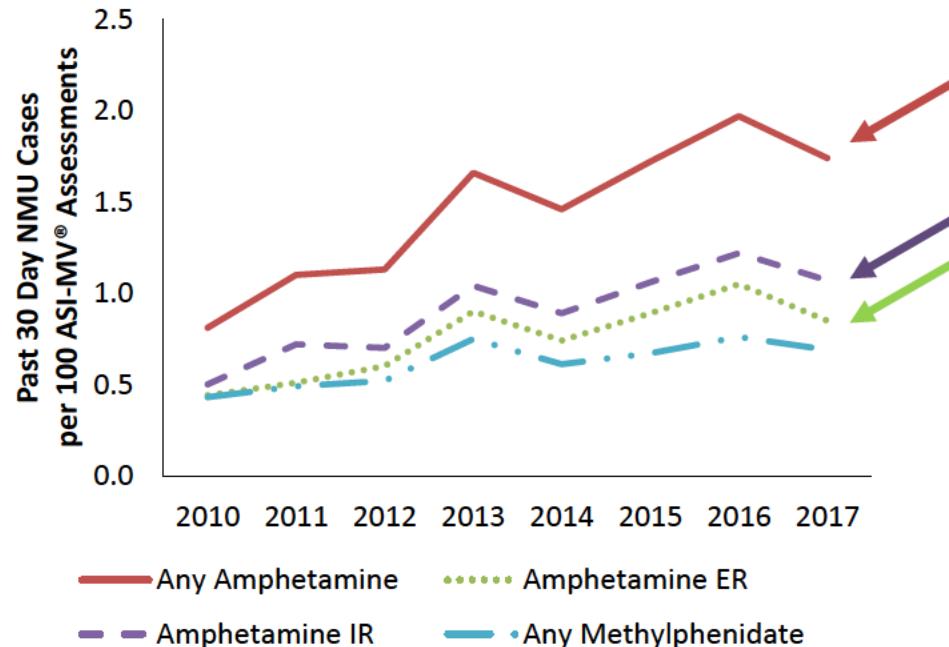
NMU = nonmedical use

Rx = prescription

NMU of Rx Stimulants among People Seeking Treatment or Being Assessed for SUDs



- Past 30-day NMU cases for selected stimulants appeared to increase from 2010 to 2017
 - Similar pattern for IR and ER amphetamines
- A nonrepresentative dynamic study population, thus trends need to be interpreted with caution



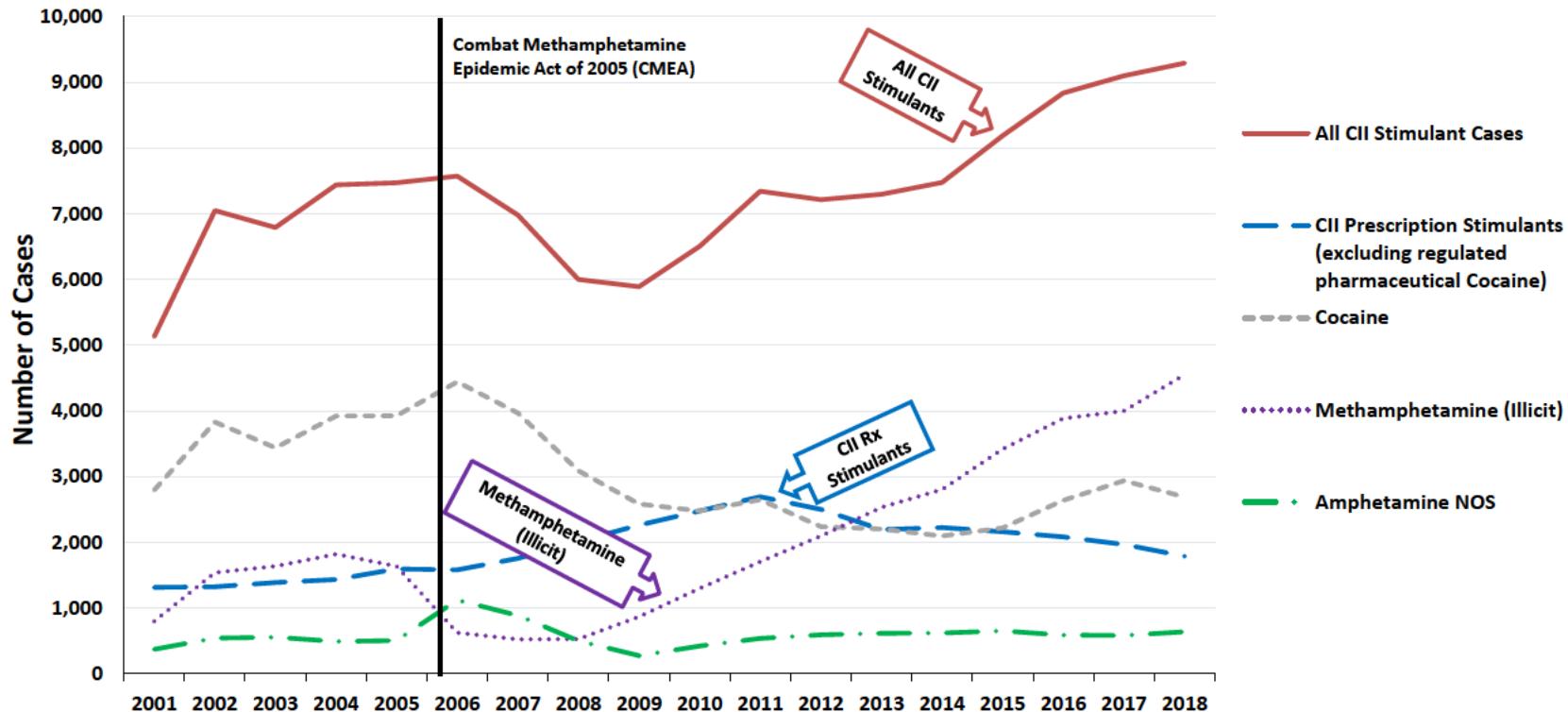
ER = extended-release

IR = immediate-release

NMU = nonmedical use

SUD = substance use disorder

National Poison Data System Cases Involving Rx Stimulant NMU Have Been Decreasing since 2011



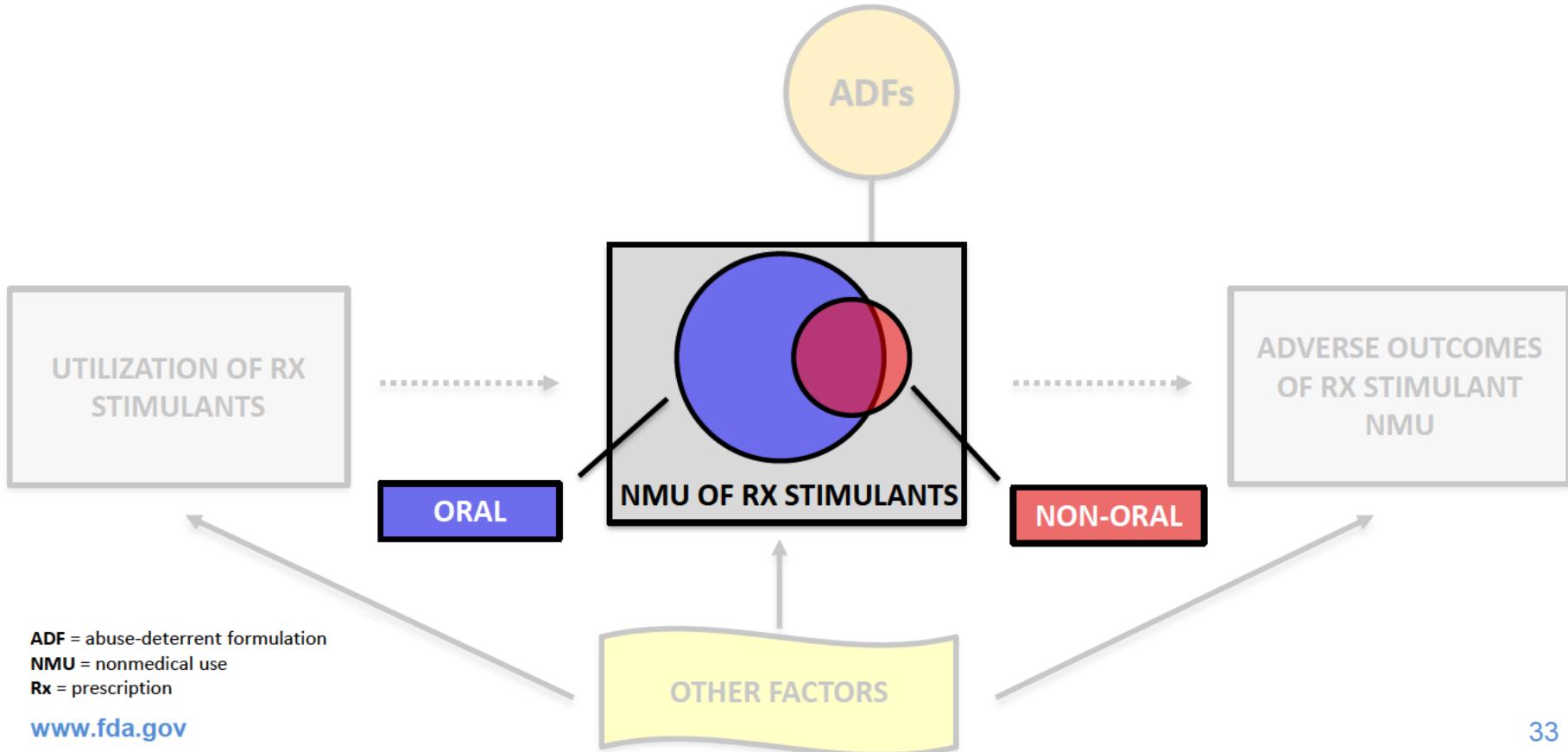
CII = Schedule II

NMU = nonmedical use

NOS = not otherwise specified

Rx = prescription

Considering Potential Public Health Impact of ADF Rx Stimulants



Contributions of Non-oral Use to the Scope and Patterns of Rx Stimulant NMU (1)



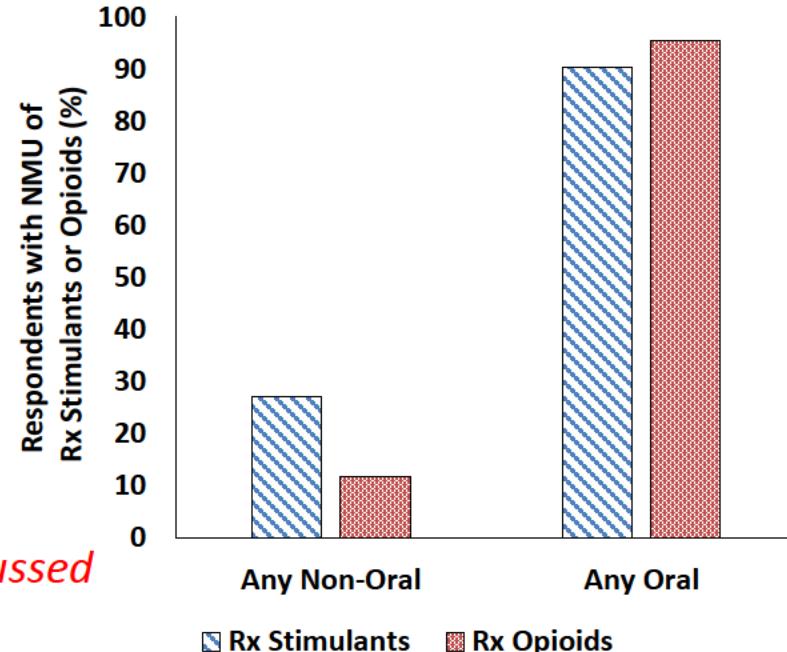
- **Vast majority of people report NMU of Rx stimulants by an oral route**
 - However, non-oral use more common in some subpopulations (e.g., individuals with SUD, college students)
- **In the general population, % snorting varies by data source**
 - 6% for National Poison Data System cases involving NMU of Rx stimulants
 - 20-30% report snorting at least some of the time across surveys
 - Smoking and injection are uncommon in the general population
- **Those entering SUD treatment more commonly report non-oral use**
 - ~40% snorting
 - 12% injection in adults (3% in adolescents)

NON-ORAL USE OF RX STIMULANTS – GENERAL POPULATION

Oral NMU of Rx Stimulants and Rx Opioids was the Most Common Route for NMU in the Applicant-Submitted Online General Population Survey

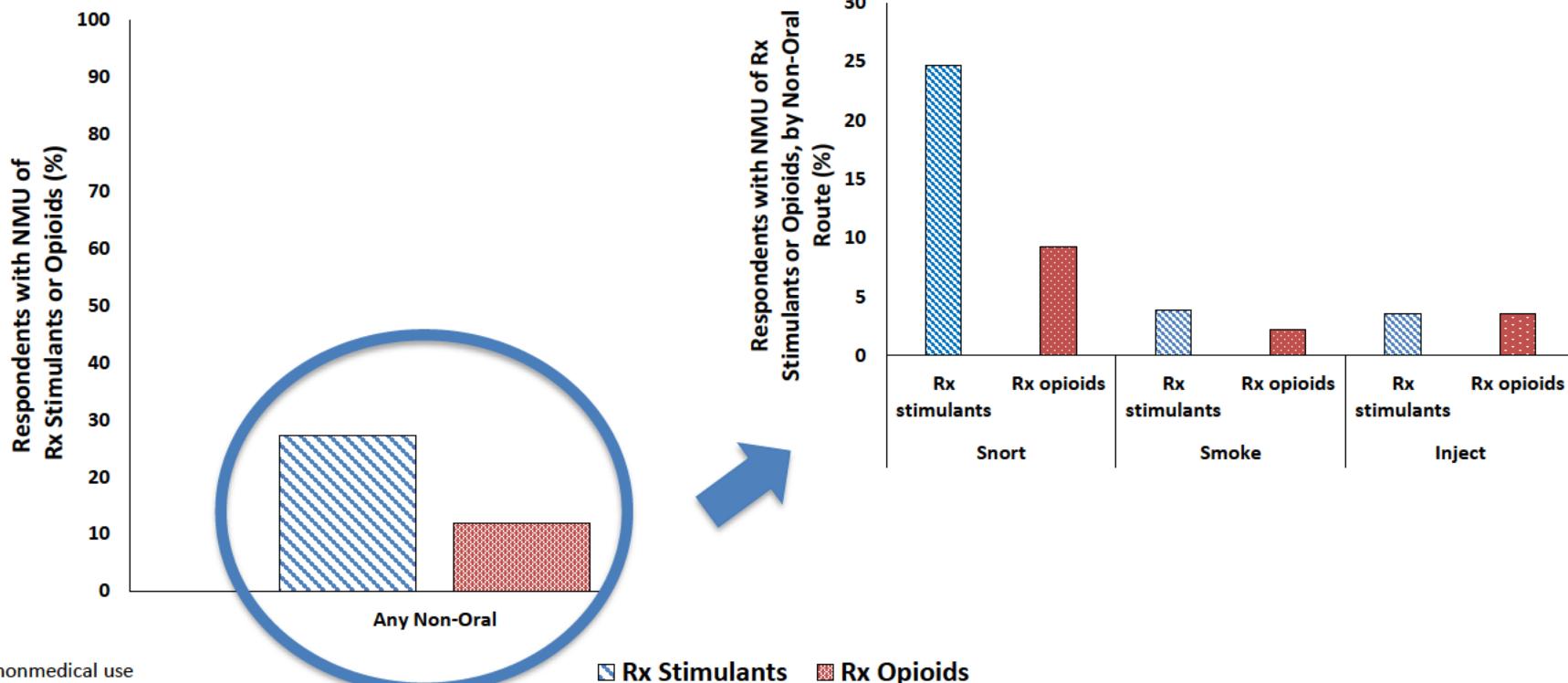


- Lifetime NMU by route, from the Applicant-submitted online survey of U.S. adults aged 18 to 49 years
- Oral was the most common NMU route (~90%) for both Rx stimulant and Rx opioids
- % Non-oral NMU of Rx Stimulants > Rx Opioids



But this comparison can be misleading—discussed in upcoming slides

Snorting Drives the Observed Difference in Non-Oral Use Between Rx Stimulants and Opioids

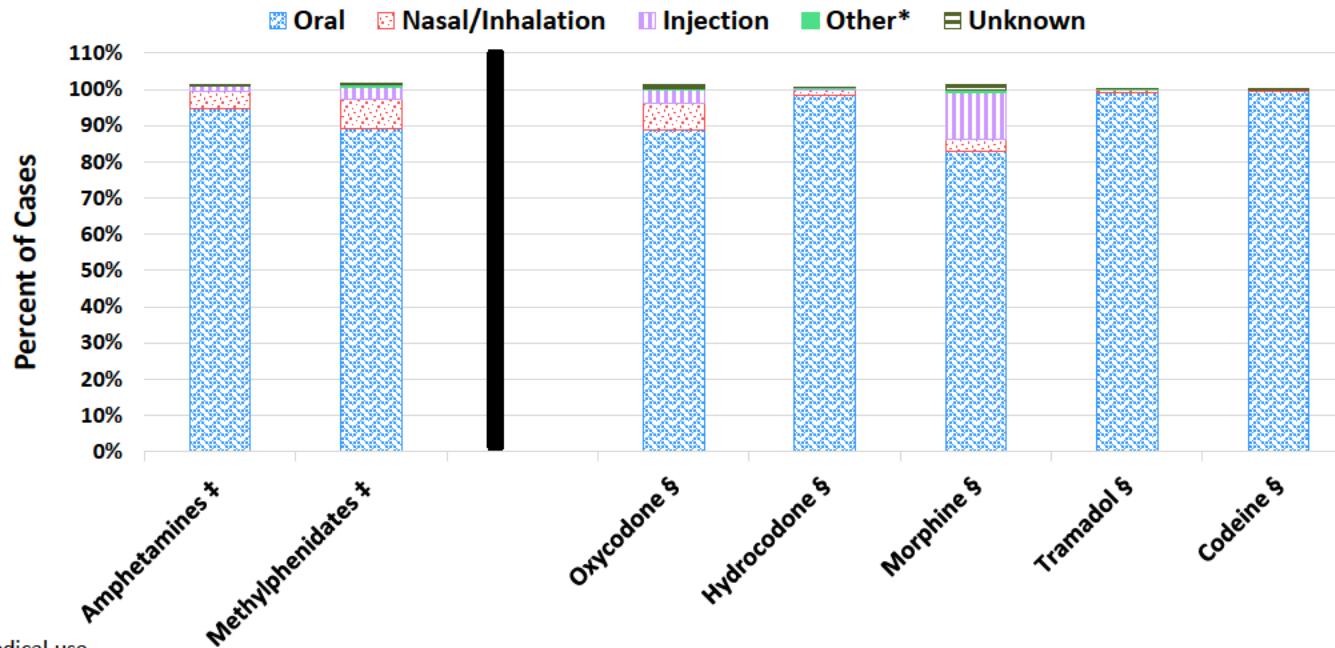


NMU = nonmedical use
Rx = prescription

www.fda.gov

Source: FDA-generated figure. Nonmedical Use of Prescription Medications among the General Population (AR19.MA004), an Applicant-submitted online survey of the general U.S. population aged 18 to 49 years conducted by the internet panel company YouGov

Oral Route Reported Most Often for NPDS Single-Substance Exposure Cases Involving NMU of Rx Stimulants and Selected Opioids



** Other includes aspiration, bite/sting, dermal, ocular, other, otic, rectal, and vaginal

'†' indicates the time period of 2001-2018

'§' indicates the time period of 2014-2018

NMU = nonmedical use

NPDS = National Poison Data System

Rx = prescription

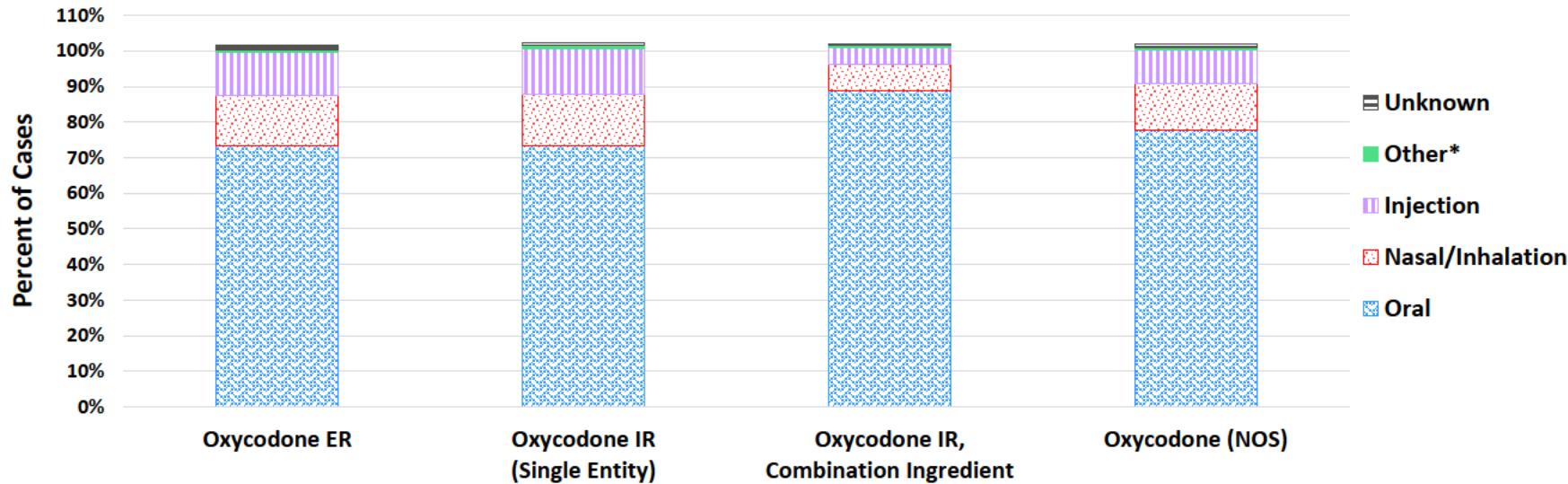
www.fda.gov

Source: FDA-generated figure. Joint Meeting of Anesthetic and Analgesic Drug Products Advisory Committee and Drug Safety and Risk Management Advisory Committee. January 15, 2020. Integrated Review of Epidemiology and Drug Utilization. Table 13. Percentage of misuse/abuse, single-substance abuse exposure calls reporting specific exposure routes for tramadol and selected other opioids[†]: U.S., NPDS, 2014-2018. Page 33. Available at: <https://www.fda.gov/media/134128/download> (accessed July 10, 2020).

Large Variation in Non-oral Intentional Abuse Routes for Single Entity and Combination Oxycodone Products



NPDS single-substance exposure cases from calls to Poison Control Centers involving intentional – abuse of prescription oxycodone, by route of exposure, 2012 to 2017



ER = extended-release

IR = immediate-release

NOS = not otherwise specified

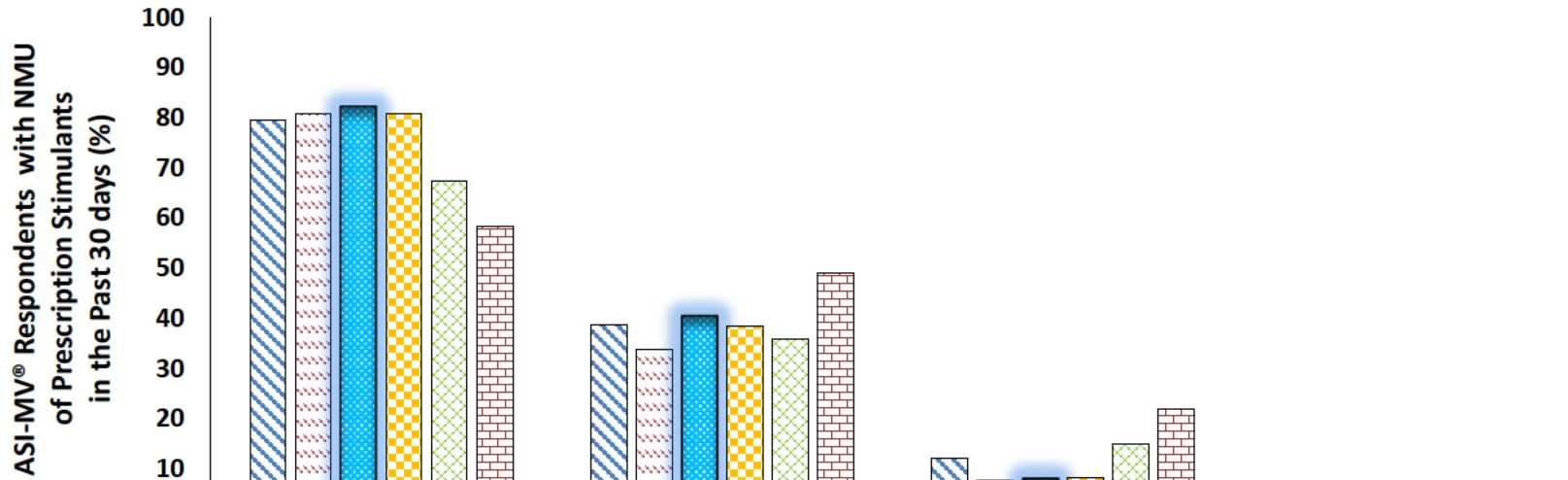
NPDS = National Poison Data System

www.fda.gov

Source: FDA-generated figure. Joint Meeting of Anesthetic and Analgesic Drug Products Advisory Committee and Drug Safety and Risk Management Advisory Committee. January 15, 2020. Epidemiology Review: Misuse and Abuse of Oxycodone and Other Opioids in the United States. Table 5. AAPCC NPDS, 2012-2017: Percentage (%) of single-substance abuse exposure calls reporting specific exposure routes for oxycodone and selected other opioids^A among individuals 12 years of age and older. Page 17. Available at: <https://www.fda.gov/media/134150/download> (accessed July 10, 2020).

NON-ORAL USE OF RX STIMULANTS – POPULATION SUBGROUPS

Oral NMU of Rx Stimulants Most Common Route, among Adults being Assessed for Substance Abuse Problems and Treatment Planning

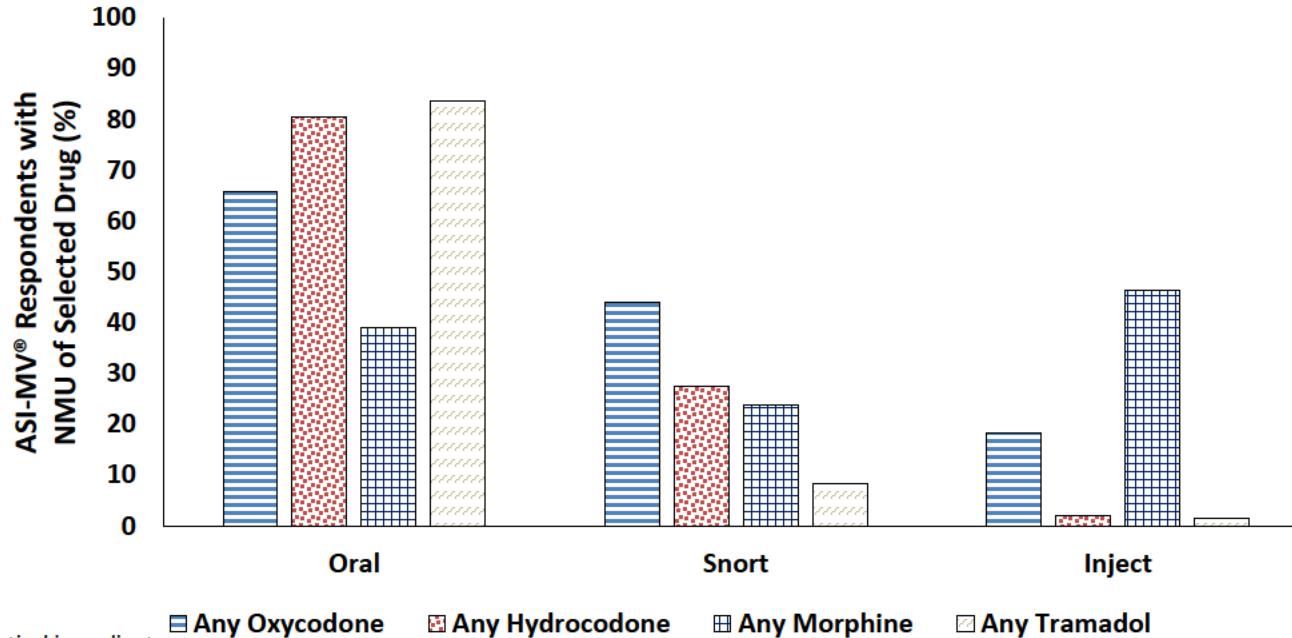


ER = extended-release
IR = immediate-release
NMU = nonmedical use
Rx = prescription
www.fda.gov

Any Rx Stimulant Amphetamine ER Amphetamine IR
Amphetamine Salt Methylphenidate ER Methylphenidate IR

Source: FDA-generated figure. Analysis of Prescription Stimulants in ASI-MV® and CHAT® (AR19.MA003), an Applicant-submitted report of people seeking treatment or being assessed for substance use disorder

Route of Rx Opioid NMU Varies Greatly by API, among Adults being Assessed for Substance Abuse Problems and Treatment Planning



API = active pharmaceutical ingredient

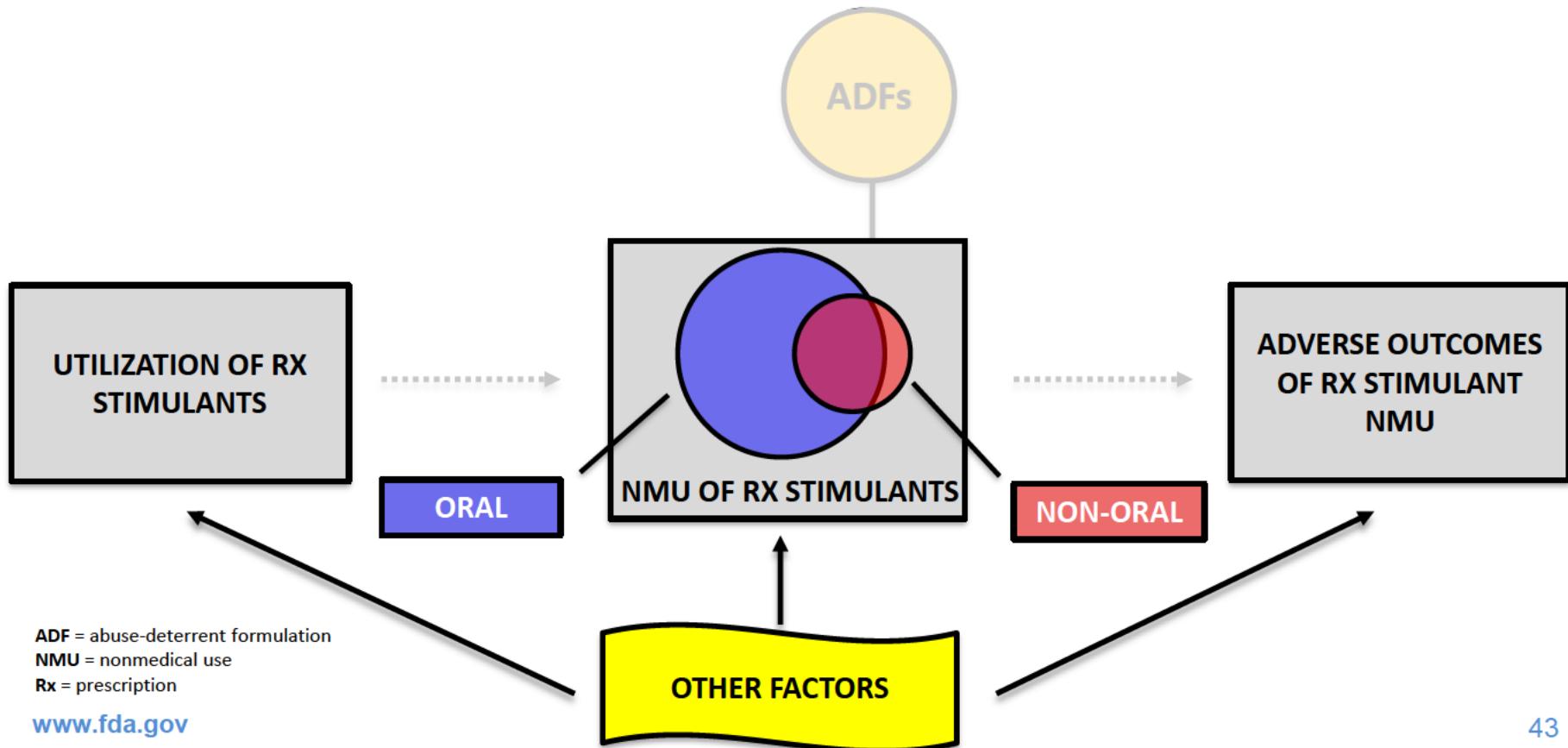
NMU = nonmedical use

Rx = prescription

www.fda.gov

Source: FDA-generated figure. Internal FDA reports from the National Addictions Vigilance Intervention and Prevention Program, Addiction Severity Index-Multimedia Version

Considering Potential Public Health Impact of ADF Rx Stimulants

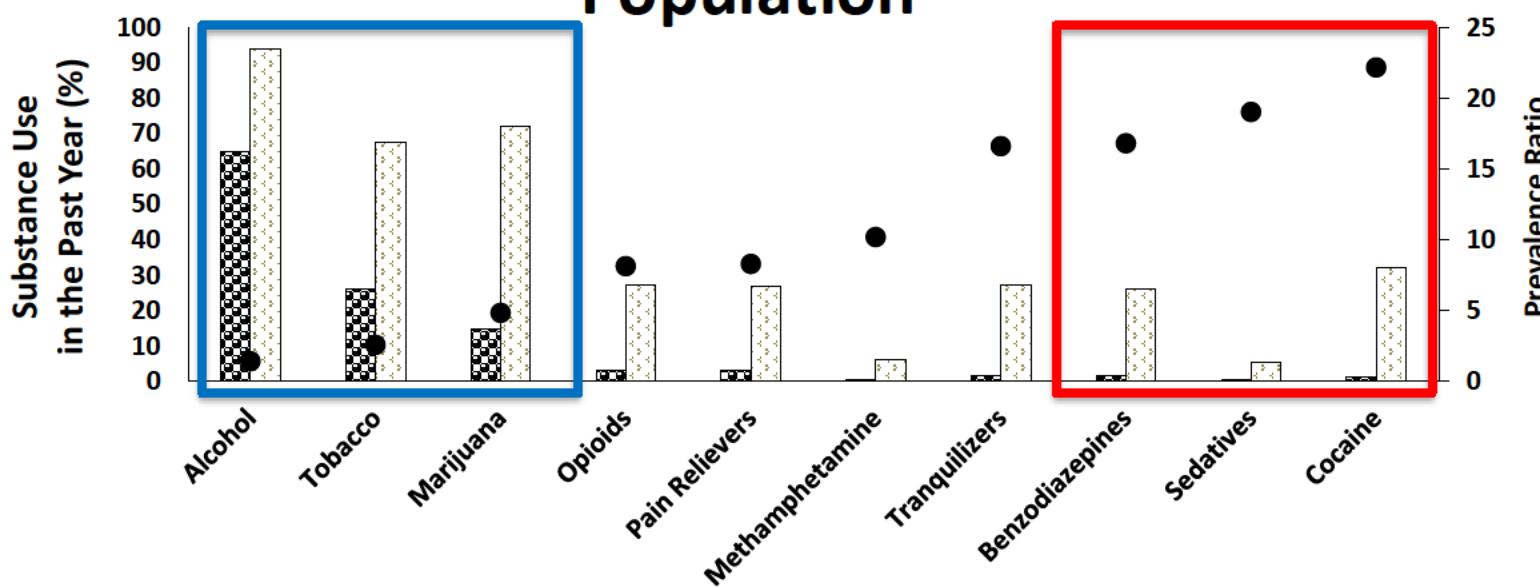


Other Factors Related to NMU of Rx Stimulants

- **Polysubstance use is common among those with NMU of Rx stimulants**
 - More common with NMU of Rx stimulants than NMU of opioid analgesics
 - Most report illicit drug use prior to NMU of Rx stimulants
 - Oral NMU *usually* proceeds non-oral NMU
- **Diversion of Rx stimulants for NMU is common**
 - Even more common than opioid analgesics
- **Most NMU is related to improving performance at work or school, staying alert or awake, or to help with concentration**
 - “Get high” was reported less often and at a similar rate reported for NMU of opioid analgesics
 - The motivation to get high was more common among those reporting non-oral NMU of Rx stimulants

POLYSUBSTANCE USE AND DRUG USE TRAJECTORY INVOLVING NMU OF RX STIMULANTS

Polysubstance Use is Common Among Individuals with NMU of Rx Stimulants, in the General Population



- ◻ Prevalence of Specific Substance Use among those without Past-Year NMU of Rx Stimulant
- ◻ Prevalence of Specific Substance Use among those with Past-Year NMU of Rx Stimulant
- Prevalence Ratio (Comparing Individuals with Past-Year NMU of Rx Stimulants to those Without)

NMU = nonmedical use

Rx = prescription

www.fda.gov

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

46

Illicit Drug Use is Common Prior to NMU of Rx Stimulants



- 90% of individuals with lifetime NMU of Rx stimulants also reported lifetime NMU of illicit drugs and/or Rx opioids¹
 - Approximately 70% initiated NMU of drugs with something other than an Rx stimulant
 - Illicit drugs, most frequently marijuana, were the most common initial drug reported for NMU
- Virtually all respondents with lifetime NMU of Rx stimulants via a non-oral route also reported use of illicit drugs²
 - 82% of respondents used an illicit drug ***prior*** to Rx stimulant NMU

Source(s): ¹Nonmedical Use of Prescription Medications among the General Population (AR19.MA004), an Applicant-submitted online survey of the general U.S. population aged 18 to 49 years conducted by the internet panel company YouGov; ²Understanding the Patterns of Prescription Medication Abuse and Progression to Non-Oral Routes of Administration (AR19.MA008), an Applicant-submitted online survey of Reddit users aged 18 years or older with a history of non-oral prescription stimulant use

Oral NMU of Rx Stimulants Frequently Occurs Prior to Non-Oral NMU, among Adults With a History of Non-Oral Rx Stimulant Use



- Applicant-submitted online survey of adult Reddit users with a history of non-oral Rx stimulant use:¹
 - 89.1% of respondents with lifetime NMU of Rx stimulants via multiple routes reported an oral route as the initial route of Rx stimulant NMU
 - 10.9% initiated with snorting
 - 0% initiated with smoking/injecting
 - Snorting was the predominant (97.9%) initial non-oral route among respondents reporting multiple routes

Oral NMU of Rx Stimulants Frequently Preceded Non-Oral NMU, BUT Not Always

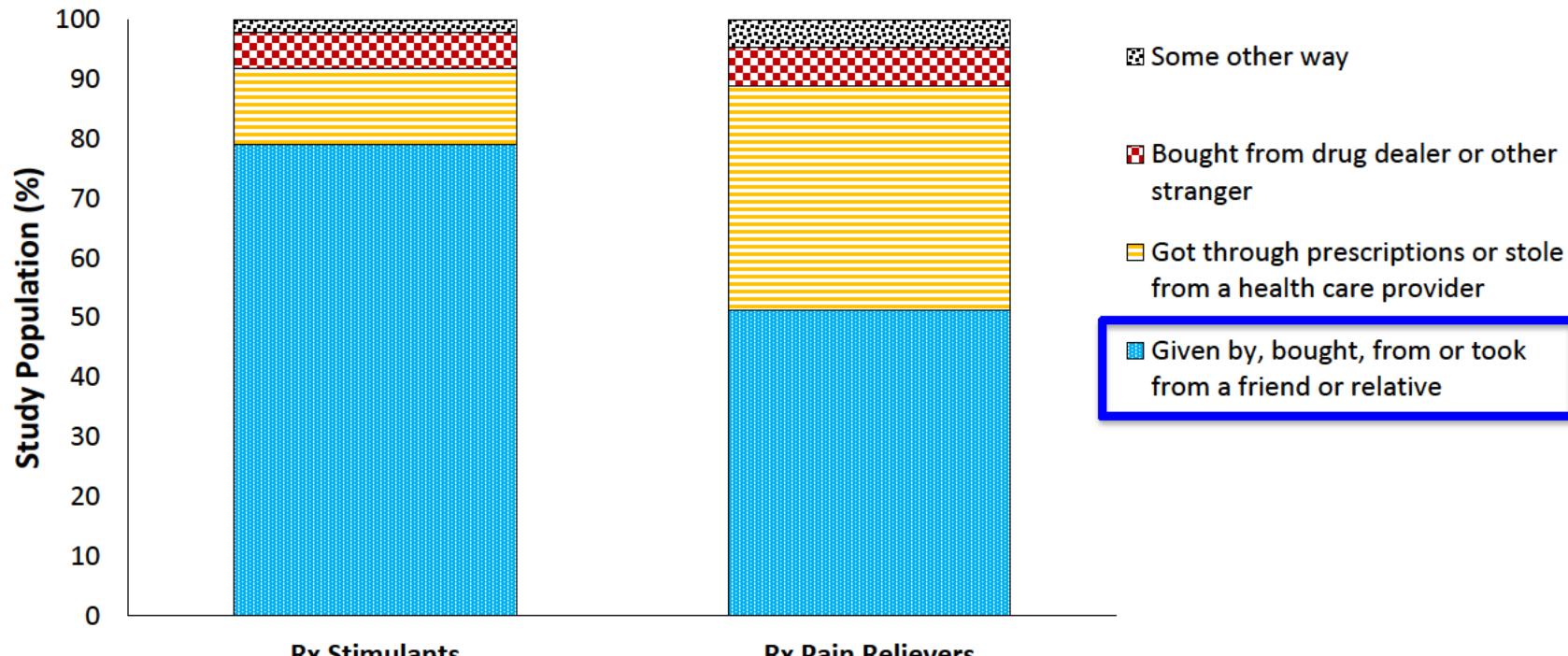


- **Drug use trajectories leading to non-oral use of prescription stimulants are diverse**
- In an Applicant-submitted report of 1,005 individuals with a history of non-oral NMU of an ADHD stimulant:¹
 - 61.5% reported using a prescription stimulant nonmedically via an oral route prior to their first non-oral use
 - 18.3% reported NMU of something other than prescription stimulants only prior to their first non-oral use of a prescription stimulant
 - 20.2% reported no prior substance use before their first non-oral use of a prescription stimulant



DIVERSION OF RX STIMULANTS

In the General Population, Diversion is More Common for Rx Stimulants Than Rx Pain Relievers



Rx = prescription

www.fda.gov

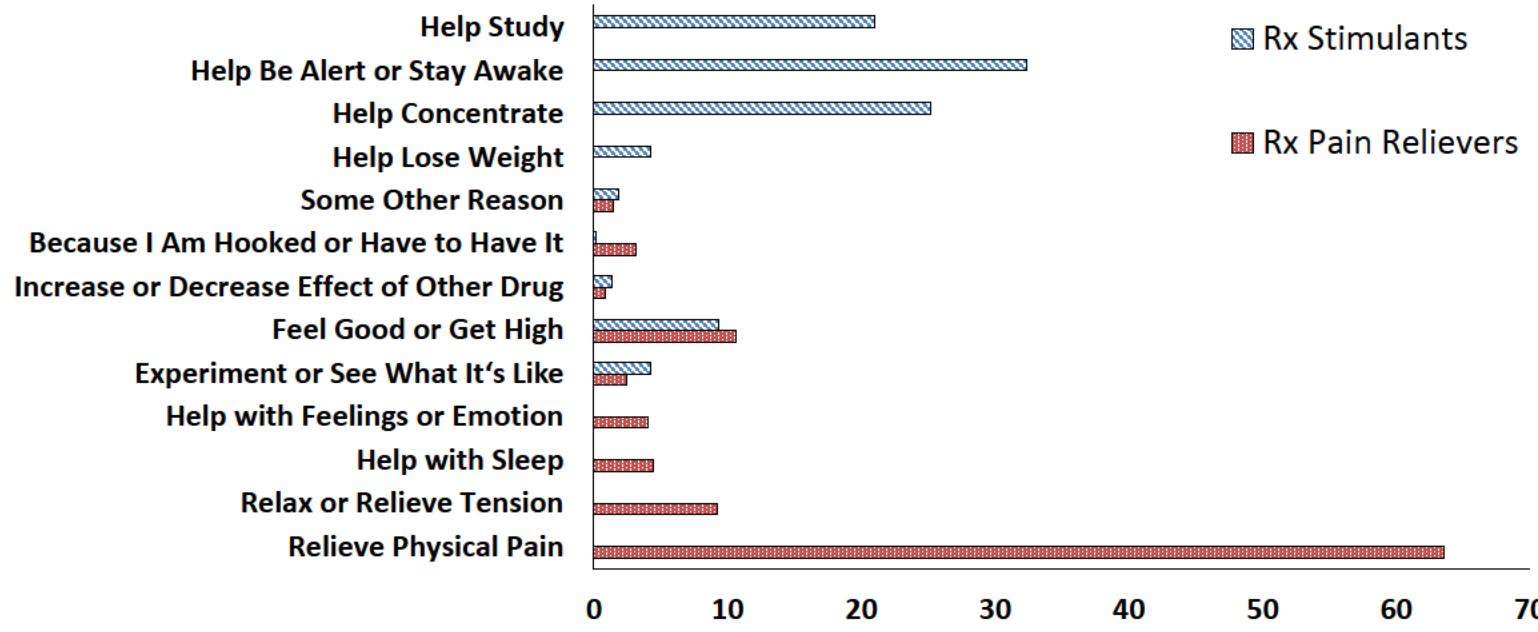
Source: FDA-generated figure from the National Survey on Drug Use and Health, 2018

51



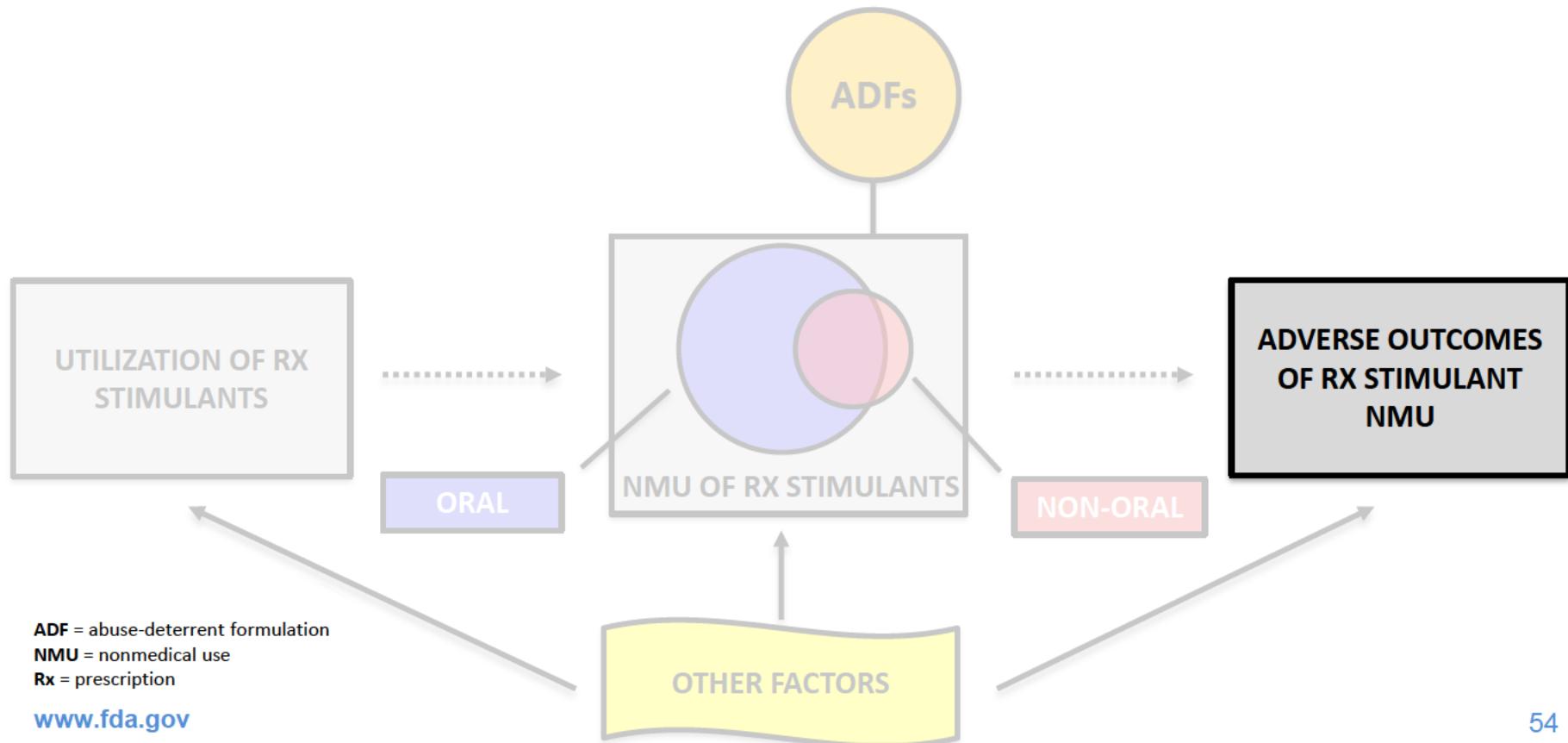
MOTIVATIONS FOR RX STIMULANT NMU

The Primary Reason for Overall NMU of Rx Stimulants, within the General Population, Align with Drug Indication



NMU = nonmedical use
Rx = prescription

Considering Potential Public Health Impact of ADF Rx Stimulants



Adverse Outcomes From Stimulant NMU: Stimulants vs Opioids



- ED visits for NMU of pharmaceutical products in 2016
 - ~3% Rx stimulants
 - ~36% Rx opioids
- Primary substance of abuse at admission to SUD treatment centers in 2017
 - Stimulants, including illicit cocaine and meth = 17% (Rx stimulants <1% of all admissions)
 - Opioids, including heroin and illicit fentanyl = 34% (Rx opioids <7% of all admissions)
- Psychostimulant-involved overdose deaths increasing rapidly, but opioid-involved overdose deaths still far higher
 - Overdose deaths in 2018:
 - Opioids = 46,802
 - Psychostimulants = 12,676
 - Cocaine = 14,666
 - Vast majority of psychostimulant deaths involve illicit methamphetamine
 - Cannot determine route of NMU from available data on deaths

Adverse Outcomes From Stimulant NMU: Non-oral vs Oral Routes



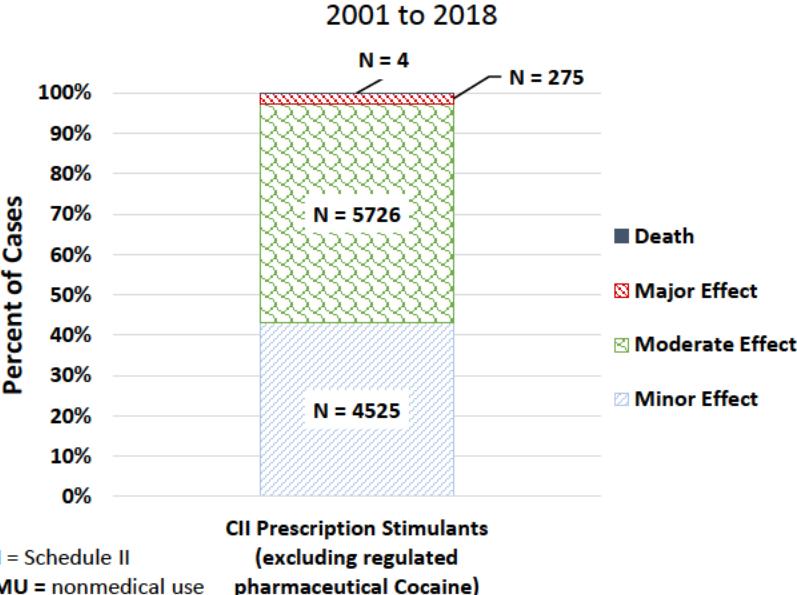
- **Injection-related harms**—endocarditis, skin infection, HIV/hepatitis, etc.
- **Inhalation-related harms** — include aspiration pneumonia, eosinophilic lung disease, and pulmonary and alveolar hemorrhage
- **But overall magnitude of harms from oral NMU >> non-oral**
 - National Poison Data System cases involving non-oral Rx stimulant use had slightly more severe medical outcomes than oral NMU cases, but the absolute number of more severe cases from non-oral

ADVERSE OUTCOMES OF RX STIMULANT NMU – OVERALL

The Majority of Rx Stimulant NMU Cases Based on Calls to U.S. Poison Centers Report a Minor or Moderate Effect



National Poison Data System Single-Substance Exposure Cases Involving NMU of Rx Stimulants, by Medical Outcome, 2001 to 2018



CII = Schedule II
NMU = nonmedical use
Rx = prescription
U.S. = United States
www.fda.gov

National Poison Data System Single-Substance Exposure Cases Involving NMU of Rx Stimulants, by Top 10 Clinical Outcomes, 2001 to 2018

CII Prescription Stimulants (excluding regulated pharmaceutical Cocaine) N = 10,530	
Clinical Outcome	% of Total Cases
Tachycardia	58.0%
Agitation	37.6%
Hypertension	23.3%
Other - Miscellaneous	21.5%
Chest pain (including noncardiac)	7.7%
Tremor	7.6%
Hallucinations/delusions	7.1%
Nausea	6.8%
Mydriasis	6.3%
Dizziness/vertigo	5.4%

Source: FDA analysis of National Poison Data System, American Association of Poison Control Centers, 2019

Emergency Department Visits Involving NMU of Rx Stimulants is Less Common than Many other Types of Pharmaceutical Products



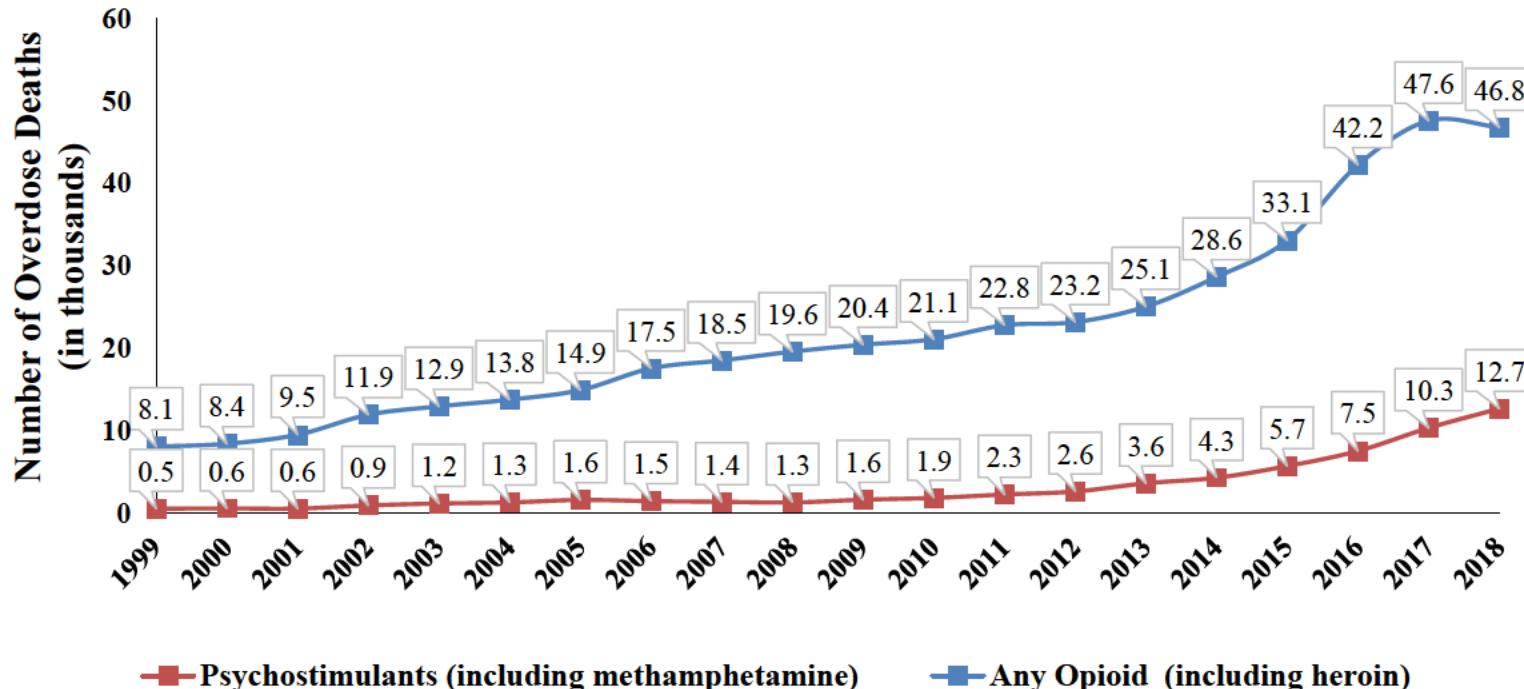
Category	Implicated alone or with other substances, annual national estimate	
	n	% total visits (95% CI)
Benzodiazepines	167,845	46.9 (42.5, 51.2)
Prescription opioids	129,863	36.2 (30.8, 41.7)
Antidepressants	24,350	6.8 (5.5, 8.1)
Cough/cold or antihistamines	23,966	6.7 (5.8, 7.6)
Nonopioid analgesics	23,758	6.6 (5.4, 7.9)
Hypnotics (non-benzodiazepine)	16,899	4.7 (3.8, 5.7)
Antipsychotics	15,874	4.4 (3.4, 5.5)
Muscle relaxants	14,731	4.1 (3.2, 5.0)
Gabapentinoids	11,669	3.3 (2.3, 4.2)
Stimulants	10,999	3.1 (1.8, 4.4)
Antihypertensives	7,824	2.2 (1.6, 2.8)
Anticonvulsants	4,828	1.3 (0.9, 1.8)
Antibiotics	4,278	1.2 (0.8, 1.6)
Other pharmaceuticals	16,775	4.7 (3.9, 5.4)
Total	358,247	100 (N/A)

NMU = nonmedical use
Rx = prescription

www.fda.gov

Source: Table adapted from Geller et al., *American Journal of Preventative Medicine*, 2019; This is a published report on a nationally representative sample of emergency department visits for adverse effects of pharmaceutical products from 2016

Overdose Deaths Involving Psychostimulants and Opioids Have Been Increasing

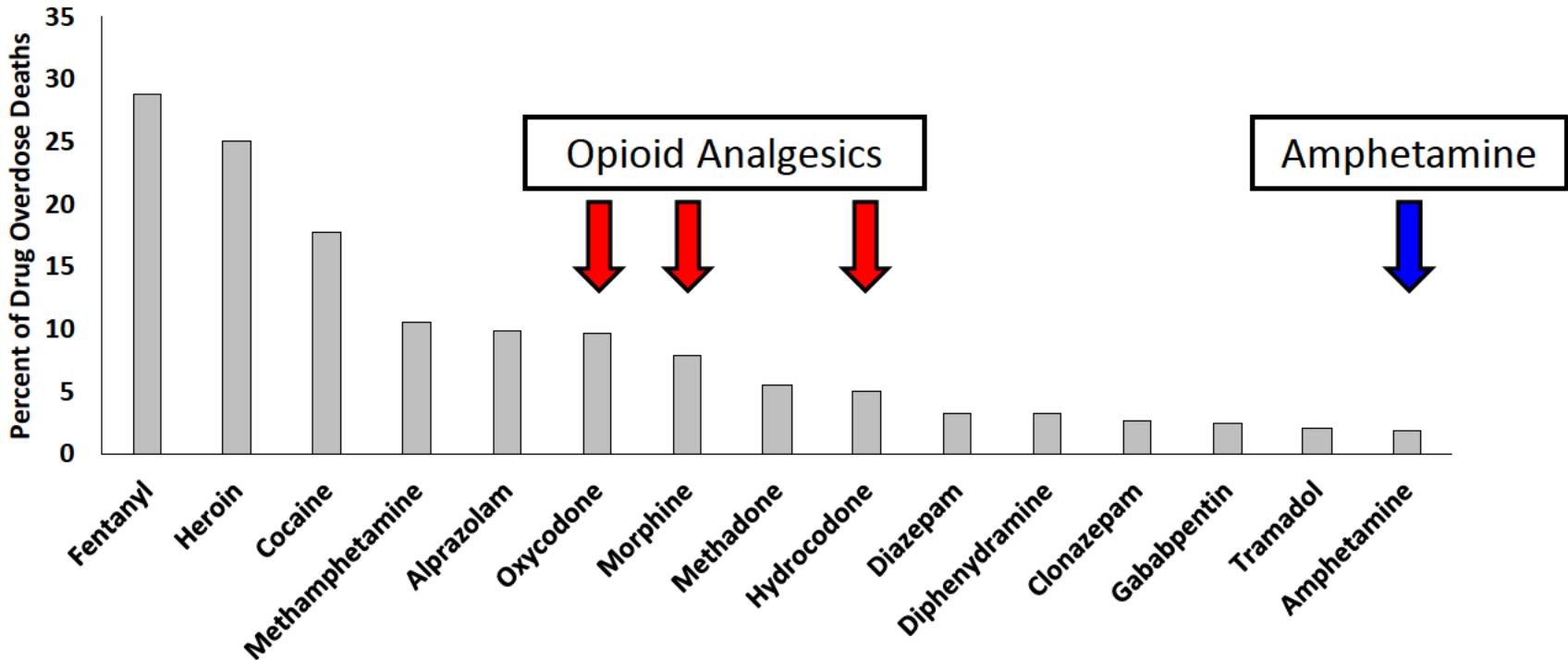


Methamphetamine was the Most Common Stimulant Reported in Deaths in the U.S. Between 2010 and 2014



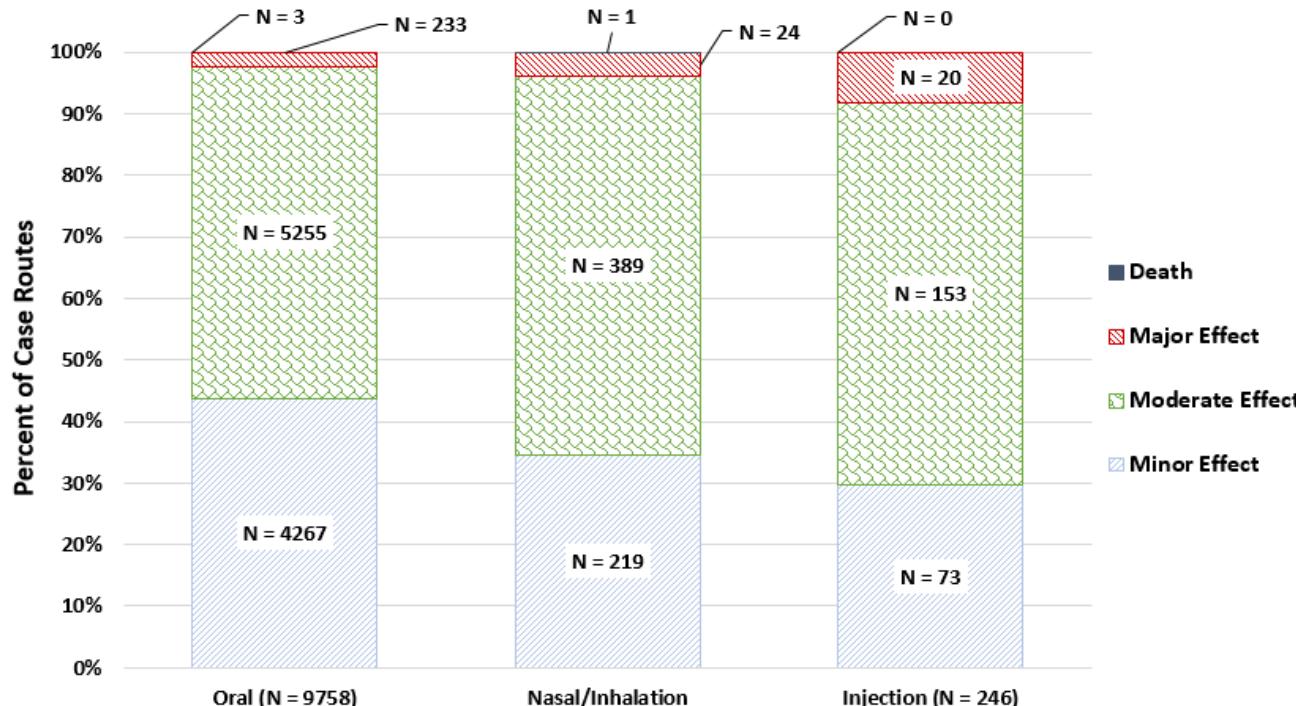
Stimulant	2010	2011	2012	2013	2014	2010–2014
Methamphetamine	2,302	2,905	3,628	4,814	5,619	19,268
Amphetamine	410	602	716	773	992	3,493
Other stimulants	29	25	33	32	47	166
Methylphenidate	25	21	28	28	40	142
Dextroamphetamine	3	4	3	4	6	20
Dexmethylphenidate	0	0	1	0	1	2
Lisdexamfetamine	1	0	1	0	0	2
Total	2,741	3,532	4,377	5,619	6,658	22,927

Top 15 Drugs Mentioned in Overdose Deaths in 2016



ADVERSE OUTCOMES OF RX STIMULANT NMU – BY ROUTE

For CII Rx Stimulants, Severe Medical Outcomes More Common in Cases that Mention Non-oral Use, but Most Were in Cases Reporting Oral NMU



CII = Schedule II

NMU = nonmedical use

Potentially Life-threatening Adverse Reactions Via Injection



Precipitating Factors	Adverse Reactions
<ul style="list-style-type: none">• Accidental intra-arterial injection• Infectious disease• Exposure to excipients• Adverse systemic effects	<ul style="list-style-type: none">• Vasoconstriction, vasospasm, endothelial damage, ischemia, thrombosis, embolism, tissue necrosis necessitating amputation• Sepsis, injection site cellulitis or abscess, bacteremia, endocarditis, hepatitis A and C, human immunodeficiency virus• Granulomatous disease (dermatologic, pulmonary, vascular), talcosis, talc retinopathy• Hyperthermia, renal failure, rhabdomyolysis, placental abruption, disseminated vasculitis

Potentially Life-threatening Adverse Reactions Via Inhalation (Intranasal/Smoking)



Precipitating Factors	Adverse Reactions	
Pulmonary complications secondary to <ul style="list-style-type: none">• Excessive exposure to stimulants• Excipients• Contaminants	Airway trauma and burns Aspiration pneumonia Asthma exacerbation Bronchiolitis obliterans Bronchitis Chronic interstitial pneumonia and fibrosis Complications of barotrauma Decreased respiratory rate Emphysema Eosinophilic lung disease Epiglottitis Epistaxis	Foreign body aspiration Granulomatous reaction Nasal septal perforation Pulmonary and alveolar hemorrhage and infarct Pulmonary edema Pulmonary hypertension Respiratory depression Rhinalgia Sinus and nasal disorder Sinusitis Tracheal stenosis

Summary of Stimulant Use and NMU Findings (1)

- Use of Rx stimulants continues to increase
- NMU remains prevalent but appears relatively stable
 - NMU of opioid analgesics remains greater than Rx stimulants, but use and NMU is decreasing
- NMU of Rx stimulants most common among young adults and college students
 - Differs from opioid analgesics
- Source of Rx stimulants for NMU most often from diversion
 - Even more than opioid analgesics
- Most NMU of Rx stimulants align with the drug's indication
 - Use to get high similar to opioid analgesics

Summary of Stimulant Use and NMU Findings (2)

- NMU of Rx stimulant associated with fewer severe harm cases (e.g., ED visits, moderate-severe NPDS cases, SUD treatment admissions, deaths) than opioid analgesics
- Oral NMU most common, with sizeable minority snorting and little smoking or injecting
 - Qualitatively similar pattern with opioid analgesics but vary by drug/formulation
- Non-oral routes (particularly injection) are associated with serious harms such as infections complications. However, oral nonmedical use contributes far more to overall harms than non-oral use
- Polysubstance use is common among individuals with NMU of Rx stimulants, especially in those with non-oral use

ADF Opioid Experience

- Low market penetration of ADF opioid analgesics (~2% of opioid analgesic market)
 - All marketed products are ER/LAs
- Challenging to assess effects in postmarket setting
- FDA conclusions from the recent advisory committee meeting on reformulated (ADF) OxyContin (oxycodone ER) postmarketing studies¹
 - Reformulation deterred OxyContin abuse by *non-oral routes* (snorting and injecting), mostly in people with more advanced SUDs
 - Overall public health impact of OxyContin's reformulation remains unclear
 - No clear reduction of overall OxyContin abuse or opioid overdose
 - Unknown impact on *initiation* of non-oral abuse or risk of addiction
 - Polysubstance use common
 - Concern about unintended consequences—e.g., substitution, including heroin

ER/LA = extended-release/long-acting

SUD = substance use disorder

www.fda.gov

Source: ¹Joint Meeting of the Drug Safety and Risk Management Advisory Committee and the Anesthetic and Analgesic Drug Products Advisory Committee Meeting Announcement. September 10-11, 2020. Available at: <https://www.fda.gov/advisory-committees/advisory-committee-calendar/september-10-11-2020-joint-meeting-drug-safety-and-risk-management-advisory-committee-and-anesthetic> (accessed September 22, 2020).

Uncertainties about Potential Public Health Impact of ADF Stimulants



- Would ADF stimulants provide meaningful public health benefit (i.e., reduce harms in patients and others)?
 - Could reduce use by riskier, but less common, non-oral routes, but do not address the most common route of NMU (oral)
 - Similar limitation for ADF opioid analgesics
 - Potential for differential impacts in different populations
 - Which patients might benefit from ADF stimulants?
 - Most obtain Rx stimulants for NMU through diversion
 - Would an ADF stimulant reduce *initiation* of non-oral routes or development of addiction?
 - Could some (e.g., those with advanced SUD, polysubstance use) substitute more dangerous illicit stimulants?
 - Excipient harms if injected?
- Can learn from ADF opioid experience, but must consider differences in patterns of use, NMU, and harms

FDA

U.S. FOOD & DRUG
ADMINISTRATION



In Vitro Studies of Proposed Abuse-Deterrent Properties, NDA 211179 AR19 (amphetamine sulfate) capsules

Andrei Ponta, Ph.D.
Chemistry, Manufacturing, and Controls (CMC) Reviewer
Office of New Drug Products (ONDP)
Office of Pharmaceutical Quality (OPQ)
Center for Drug Evaluation and Research (CDER)
U.S. Food and Drug Administration (FDA)
Advisory Committee Meeting

AR19 (amphetamine sulfate) capsules

- Immediate release amphetamine sulfate capsules
- 2.5 mg, 5 mg, 10 mg, 15 mg, 20 mg, 30 mg, and 40 mg strengths
- Administered orally or by opening the capsules and sprinkling the pellets over food
- Abuse deterrent properties primarily imparted by the excipient polyethylene oxide (PEO) 7,000,000
- Performed in vitro abuse-deterrent studies (Category 1 Studies)
 - Comparator Product: FDA approved amphetamine sulfate immediate release tablet (10 mg)

Category 1 Studies

- Physical Manipulation (Particle Size Reduction)
- Small and Large Volume Extractability and Syringeability Studies
- Large Volume Extraction Studies
- Smoking Studies

Physical Manipulation

- Goal of the study is to manipulate the product to the point of defeating its abuse deterrent properties.
 - Variety of mechanical tools used (e.g., cutting, crushing, grating, grinding)
 - With and without pretreatment (e.g., heating, cooling)
- Generally particle sizes of less than 500 microns are considered to be insufflatable

Overall Physical Manipulation Results

- Without pretreatment
 - Comparator:
 - Less than 500 microns: up to **98.4%**
 - Less than 1000 microns up to **99.6%**
 - AR19
 - Less than 500 microns: up to **75.6%**
 - Less than 1000 microns up to **88.8%**
- With pretreatment
 - Less than 500 microns: up to **87.8%**
 - Less than 1000 microns: up to **99.7%**

Manipulation Method	Pretreatment	Particle Size (%)		
		Greater than 1000 microns	500 – 1000 microns	Less than 500 microns
Method 1	None	1.1	23.2	75.6
Method 2	None	15.7	37.5	46.8
Method 3	None	0.4	57.4	42.2
Method 1	Yes	0.3	11.9	87.8
Method 1	Yes	4.5	47.8	47.7
Method 1	Yes	0.8	27.3	71.9

If 75% of a 40 mg capsule is reduced to less than 500 microns, this equates to about 30 mg of insufflatable amphetamine.

Office of Testing and Research (FDA)

- Performed confirmatory physical manipulation studies
- Results largely in line with Applicant's results
 - Pretreatment did not have a significant impact on particle size
 - When totaling all particle fractions, amphetamine sulfate recovery was at least 95% regardless of manipulation tool
 - Physical manipulation does not degrade amphetamine sulfate

Extractability and Syringeability Studies

- Explored methods to obtain a syringeable solution
 - Small Volume (less than 10 mL)
 - With and without pretreatment
 - Multiple solvents
 - Various extraction times and temperatures
 - Intact and manipulated product
 - Large Volume (greater than 10 mL)
 - Similar to small volume extraction, except using a larger volume of solvent
 - After completing extraction, volume reduced to a syringeable amount

Extractability and Syringeability Studies

- Small volume results without pretreatment in various solvents
 - Up to ~95% of amphetamine sulfate from the 10 mg strength comparator was extracted
 - Up to ~15% of amphetamine sulfate (6 mg) from the AR19 40 mg strength was extracted

Extractability and Syringeability Studies

- Small volume results for AR19 capsules (40 mg)
 - With pretreatment

Particle Size Reduction	Amphetamine	
	%	mg
None	27.8	11.12
None	24.2	9.68
Yes	24.4	9.76
Yes	31.4	12.56
Yes	50.2	20.08
Yes	45.5	9.1
Yes	47.5	9.5

Extractability and Syringeability Studies

- Large volume summary
 - Up to 31.5% of amphetamine (12.6 mg) was recovered
- Extraction from multiple capsules was largely not feasible
 - Addition of a 2nd 40 mg capsule led to an additional ~3 mg amphetamine
 - Addition of 3rd, 4th, 5th, capsules did not lead to any additional amphetamine extracted

Large Volume Extraction Studies

- Determined ability to produce a drinkable solution of drug product
 - Close to 100% of the amphetamine sulphate from both AR19 capsules and the comparator product was extracted

Smoking Studies

- Manipulated comparator product, and manipulated drug product (5 mg, 20 mg, and 40 mg) smokeability was assessed
- Yield was low; not expected to be a common method of non-medical use
 - ~2.5% of amphetamine sulfate was volatilized from manipulated comparator product
 - 2% – 10% of amphetamine sulfate was volatilized from manipulated drug product

Conclusions

- Physical Manipulation (Particle Size Reduction)
 - Comparator product:
 - 82.5 – 98.4% was reduced to a particle size less than 500 microns, without pretreatment
 - AR19
 - Without pretreatment, up to 75.6% was reduced to a particle size less than 500 microns, and up to 88.8% of particles were less than 1000 microns
 - With pretreatment, up to 87.8% was reduced to a particle size less than 500 microns, and up to 99.7% of particles were less than 1000 microns

Conclusions Cont.

- Small Volume Extractability and Syringeability Studies
 - Comparator
 - Up to 90% amphetamine was extracted without pretreatment
 - AR19 40 mg
 - Extraction without pretreatment: up to ~15% amphetamine extracted
 - Extraction with pretreatment: up to ~50% (~20 mg) amphetamine extracted
 - Extraction from multiple capsules was largely not feasible
- Large Volume Extractability and Syringeability Studies
 - Syringeable amphetamine recoveries were similar or lower than those using small volumes

Conclusions Cont.

- Large Volume Extraction Studies
 - Both AR19 and the comparator product were able to produce a drinkable solution containing high amounts of amphetamine sulfate
- Smoking Studies
 - Neither AR19 nor the comparator product produced significant amounts of volatilized amphetamine sulfate





Evaluation of the Purported Abuse-Deterrent Properties of AR19

SHALINI BANSIL, M.D.
MEDICAL OFFICER
CSS/OCD/CDER

Psychopharmacologic Drugs Advisory Committee (PDAC) and Drug Safety and Risk Management (DSaRM) Advisory Committee Meeting

October 8, 2020

Overview of Abuse-Deterrent Drug Products

- Prescription drug products can be abused in a number of ways, for example physically manipulated to a form that can be self-administered by an unintended route
- Abuse-deterrent formulations (ADFs) are products that are expected to make abuse by particular routes more difficult
- ADFs incorporate technologies to address abuse
 - For example, physical/chemical barriers to achieve a sample suitable for abuse
- ADFs are evaluated relative to a relevant comparator to determine if the abuse-deterrent (AD) property will lead to a meaningful reduction in abuse
- It is important to note that ADFs...
 - Are **not** abuse proof
 - Can **still be abused** by all routes to some degree
 - Do not alter the abuse potential of the active ingredient

Evaluation of Abuse-Deterrent Opioid Analgesics



- To date, only opioid analgesic products have been approved with labeling claims describing abuse-deterrent properties
 - Products evaluated consistent with the principles outlined in FDA's 2015 guidance for industry, ***Abuse-Deterrent Opioids - Evaluation and Labeling***
 - It was discussed with the Applicant that the Guidance, although specific to opioid analgesics, describes premarket methodologies that may be applied to other drug classes
- Phased evaluation (based on categories of studies) outlined in the guidance was used to evaluate AR19, at this stage only Premarket Evaluation:
 - Laboratory-based in vitro manipulation and extraction studies (Category 1)
 - Pharmacokinetic studies (Category 2)
 - Human abuse potential studies (Category 3)
- Postmarket Evaluation occurs only following approval and marketing of an ADF:
 - Analysis of postmarket data to assess the impact of an ADF on actual abuse (Category 4)

Abuse-Deterrent Evaluation of AR19

By route of abuse:

- Oral: no AD property intended, no studies to evaluate oral abuse potential of AR19, an immediate-release oral dosage form
- Intranasal: a human abuse potential (HAP) study was conducted
 - Best manipulation method to prepare sample for insufflation was identified from Category 1 studies
- Smoking: in vitro manipulation studies were conducted
- Intravenous: in vitro manipulation studies were conducted

In Vitro Assessment of AR19 for the IV and Smoking Routes

IV route

- In vitro studies provide data on the amount of amphetamine extracted into a solution suitable for injection
- Interpretation of in vitro studies requires understanding of a dose-response curve for reinforcing effects in human abuse potential studies to determine the minimum reinforcing dose
 - The Applicant did not conduct a pilot study for this purpose
- Based on the Agency's literature search, a 10 mg amphetamine dose administered in 1 mL over 1 minute is expected to produce reinforcing subjective effects
- In vitro manipulation studies demonstrated that it was possible to form a solution containing 10 mg or greater of amphetamine for intravenous use

Smoking route

- Vaporization studies demonstrated that ≤10 % of amphetamine was volatilized from manipulated AR19; this was not appreciably different from the marketed comparator product

Study AR19.001: Human Abuse Potential and Pharmacokinetic Study

- **Design:** Randomized, double-blind, active- and placebo-controlled, two-part study
- **Objective:** To evaluate the intranasal (IN) abuse-deterrent effects of manipulated AR19 compared with amphetamine active pharmaceutical ingredient (API)
- **Population:** Nondependent individuals who recreationally use stimulants

Study AR19.001: Key Inclusion Criteria

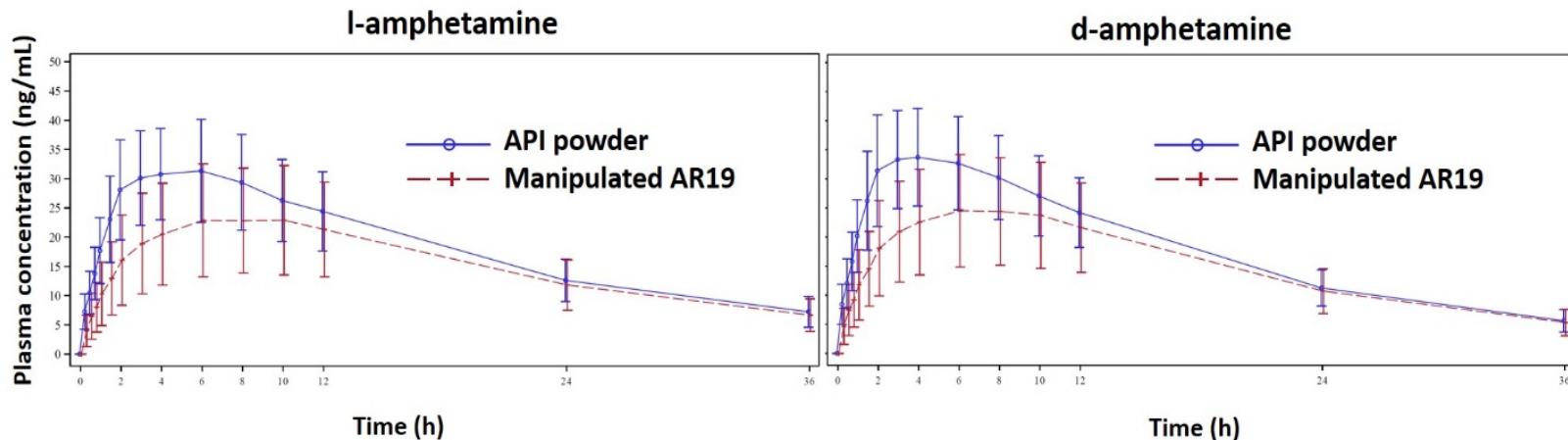
- Current use of stimulants
 - Individuals with recreational (nontherapeutic) stimulant use (i.e., for psychoactive effects) at least 10 times in their lifetime and at least 1 time in the 12 weeks before screening
- Experience with IN recreational (nontherapeutic) drug use at least three times in year prior to screening

Study AR19.001: Study Conduct

- Part A: Dose selection: 20 mg, 30 mg, and 40 mg of amphetamine API investigated
 - 40 mg selected
- Part B:
 - Qualification Phase
 - To identify subjects able to discriminate between 40 mg IN amphetamine API and placebo
 - Treatment Phase
 - Manipulated AR19 40 mg
 - Amphetamine API 40 mg
 - Placebo

Study AR19.001: Pharmacokinetic (PK) Results

- PK samples were taken pre-dose and at selected times post-dosing
- Average plasma concentration-time profiles for *l*-amphetamine and *d*-amphetamine following single-dose intranasal administration of 40 mg manipulated AR19 and 40 mg amphetamine sulfate API powder
- PK findings alone are not sufficient to determine AD effects



Study AR19.001: Pharmacodynamic Assessments

- Drug Liking, Take Drug Again, Overall Drug Liking
 - Measured on a bipolar 0 to 100 visual analog scale (VAS)

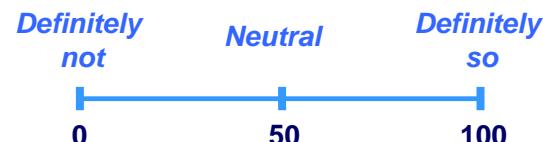
Drug Liking VAS

At this moment, my liking for this drug is:



Take Drug Again VAS

I would take this drug again



Overall Drug Liking VAS

Overall, my liking for this drug is:



- High
 - Measured on a unipolar 0 to 100 VAS

High VAS

At this moment, I feel high



Study AR19.001

Primary Endpoint

- The maximum (peak) effect (i.e., Emax) for Drug Liking VAS (“at this moment”)

Secondary Endpoints

- Emax Overall Drug Liking (ODL) VAS (“Overall, my liking for this drug is”)
- Emax Take Drug Again (TDA) VAS (“I would take this drug again”)
- Emax High VAS (“At this moment, I feel high”)

Study AR19.001: Study Validation

- Completer population consisted of the 37 subjects that completed all three treatment periods
- Study validation test was performed on the completers population
 - Required at least a 15 point difference on the primary endpoint of Emax of Drug Liking between amphetamine API 40 mg and placebo at the prespecified alpha level of 0.025
- Study was not validated based on this analysis

Study AR19.001: Study Validation

Primary Analysis Results on Drug Liking E_{max} (n=37)

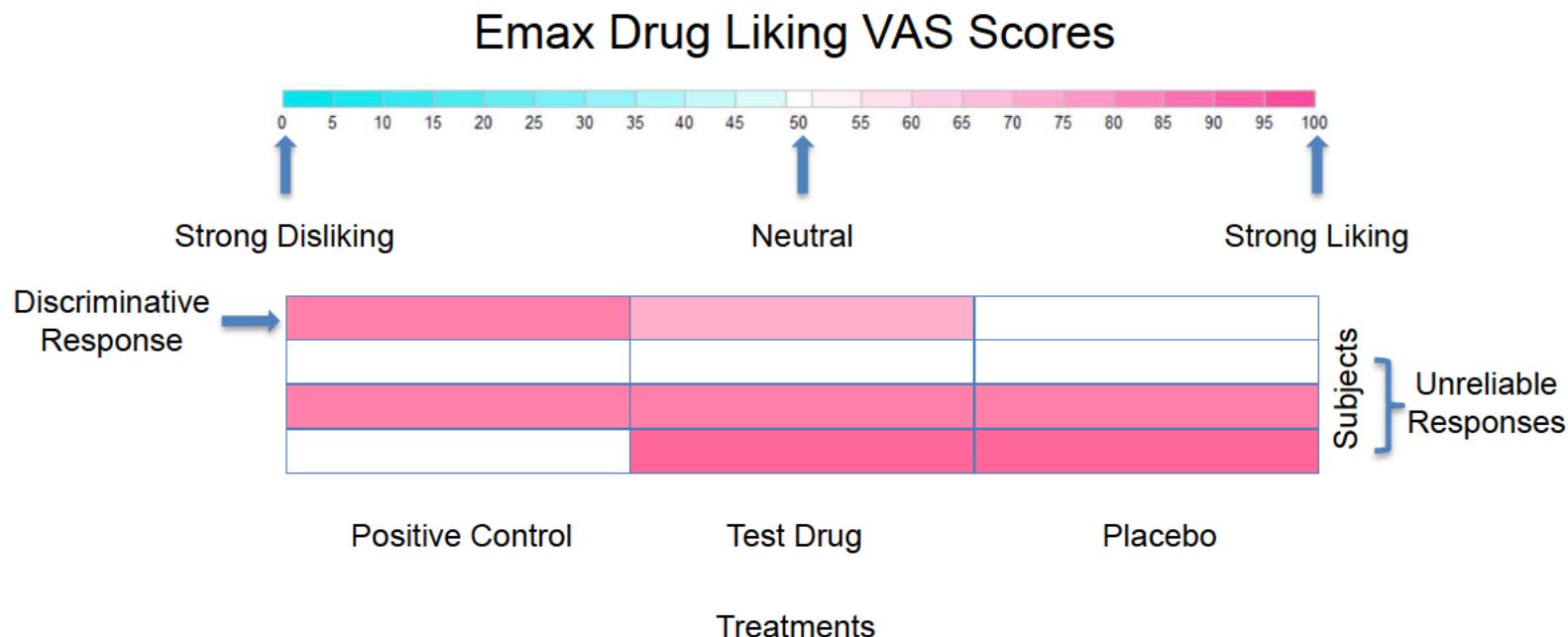
Comparison	Med Diff	IQR	Test Value	p-Value	95% CI	
					LCL	UCL
Amphetamine API 40 mg vs Placebo	23.0	11, 37	15	0.0877	13.1	32.0

Med Diff: Median difference; IQR: interquartile range; LCL: lower confidence limit;
UCL: upper confidence limit; CI: confidence interval

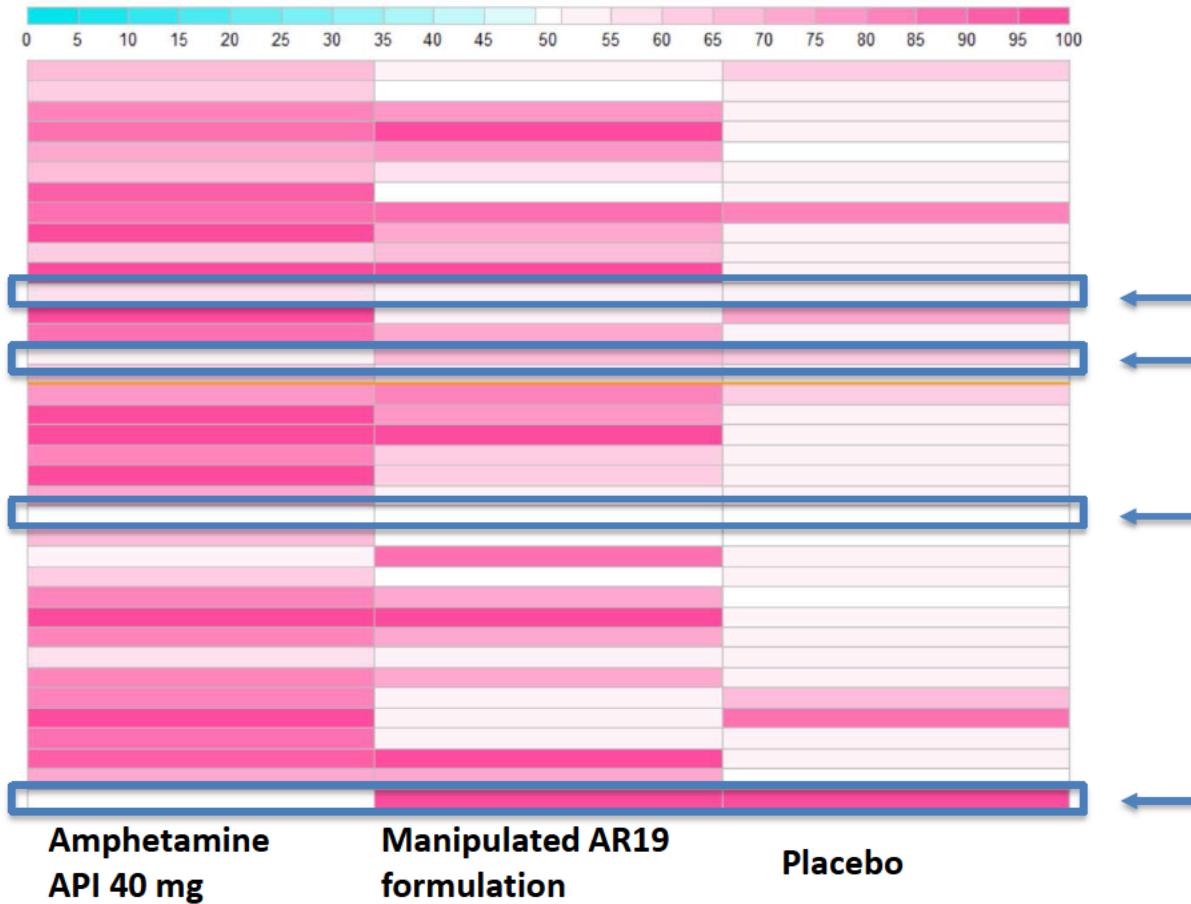
Study AR19.001: Exploratory Analyses

- Prespecified criteria may be used to remove subjects from the analyses, including analysis for study validation, who did not provide reliable responses; however, the Applicant did not prespecify these criteria
- The Applicant conducted a post-hoc analysis excluding the one subject they determined to have likely contributed to study validation failure
 - Analysis not acceptable
- The Agency conducted a separate post-hoc exploratory analysis and excluded four subjects with unreliable responses using what would have been acceptable prespecified criteria
 - We defined this as the modified completers population (n=33) and used this population for all further analysis of the study results

Hypothetical Heat Map for Emax Drug Liking VAS by Treatment



Study AR 19.001: Emax Drug Liking—Heat Map View



Study AR19.001: Agency Exploratory Analysis of Study Results

- Two main types of analyses
 - Analysis of difference in means between manipulated AR19 and amphetamine API on the primary and secondary endpoints
 - Performed consistent with the Applicant's primary analysis:
 - Not designed to simply detect a difference in means between treatment groups
 - Statistical test on the difference in means using a threshold of at least a 10% reduction with manipulated AR19 as compared to amphetamine 40 mg
 - Responder analyses on the primary and secondary endpoints
 - Based on the hypothesis that the majority of subjects (>50%) would be responders, defined as having at least a 10% reduction for manipulated AR19 compared to amphetamine 40 mg

Study AR19.001: Exploratory Primary Analysis, Modified Completer Population (n=33)



- Analysis of Drug Liking Emax between positive control and placebo passed the validation test
- Analysis of Drug Liking Emax between manipulated AR19 and amphetamine API 40 mg did not reach nominal statistical significance ($p=0.0311$; prespecified alpha level of 0.025)
- Drug Liking Emax for manipulated AR19 was greater than that of placebo

Exploratory Primary Analysis Results on Drug Liking Emax for the Modified Completer Population (n = 33)

TRT	LSMean	SE
Placebo	55.0	1.8
Amphetamine 40 mg	77.9	2.8
Manipulated AR19	68.7	2.9

TRT, treatment; LSMean, least square mean; SE, standard error

Study AR19.001: Summary of Agency's Exploratory Analyses for AR19*



	Drug Liking (Emax)	Overall Drug Liking (Emax)	Take Drug Again (Emax)	High (Emax)
Difference in means analysis: AR19 vs. Amphetamine API	Failed	Passed at the 10% level	Passed at the 20% level	Passed at the 45% level
Responder analysis: AR19	Failed	Failed	Failed	Passed

*These analyses are post hoc and exploratory; any statistical findings are considered nominal

Study AR19.001: Overview of the Analyses Conducted



- **Completer population (n=37); prespecified population**
 - Analysis failed the validation test, therefore, not appropriate to analyze the data for this population further
 - 9% is not the prespecified margin (10% margin was prespecified)
- **Applicant's modified completer population (n=36); post-hoc exploratory analysis**
 - The Applicant stated that the analysis was validated; however, the Agency did not agree with their statistical approach
- **Agency's modified completer population (n=33); post-hoc exploratory analysis**
 - Nominally passed the validation test
 - Primary analysis did not reach nominal statistical significance
 - Responder analysis on the primary endpoint did not reach nominal statistical significance

Overall Summary of Abuse-Deterrent Findings

- Based on the immediate release (IR) properties of the AR19 formulation, AR19 was not intended to, and will not, deter abuse by the oral route, which is the most common route of amphetamine prescription drug abuse
- In vitro manipulation studies demonstrated that it is feasible to obtain a solution for injection containing a reinforcing dose of amphetamine, under the conditions reported by the Applicant
- The IN HAP study does not provide convincing evidence that the formulation employed for AR19 has significant abuse-deterrent effects, as compared to amphetamine sulfate, when administered by the IN route





Nonclinical Safety Assessment of AR19 Capsule Excipients

Shiny V. Mathew, PhD, DABT
LCDR, USPHS
Pharmacology/Toxicology (P/T) Reviewer
Division of P/T-Office of Neuroscience (Psychiatry Division)
Center for Drug Evaluation and Research

**Psychopharmacologic Drugs Advisory Committee (PDAC) and
Drug Safety and Risk Management (DSaRM) Advisory Committee Meeting**

October 8, 2020

Overview

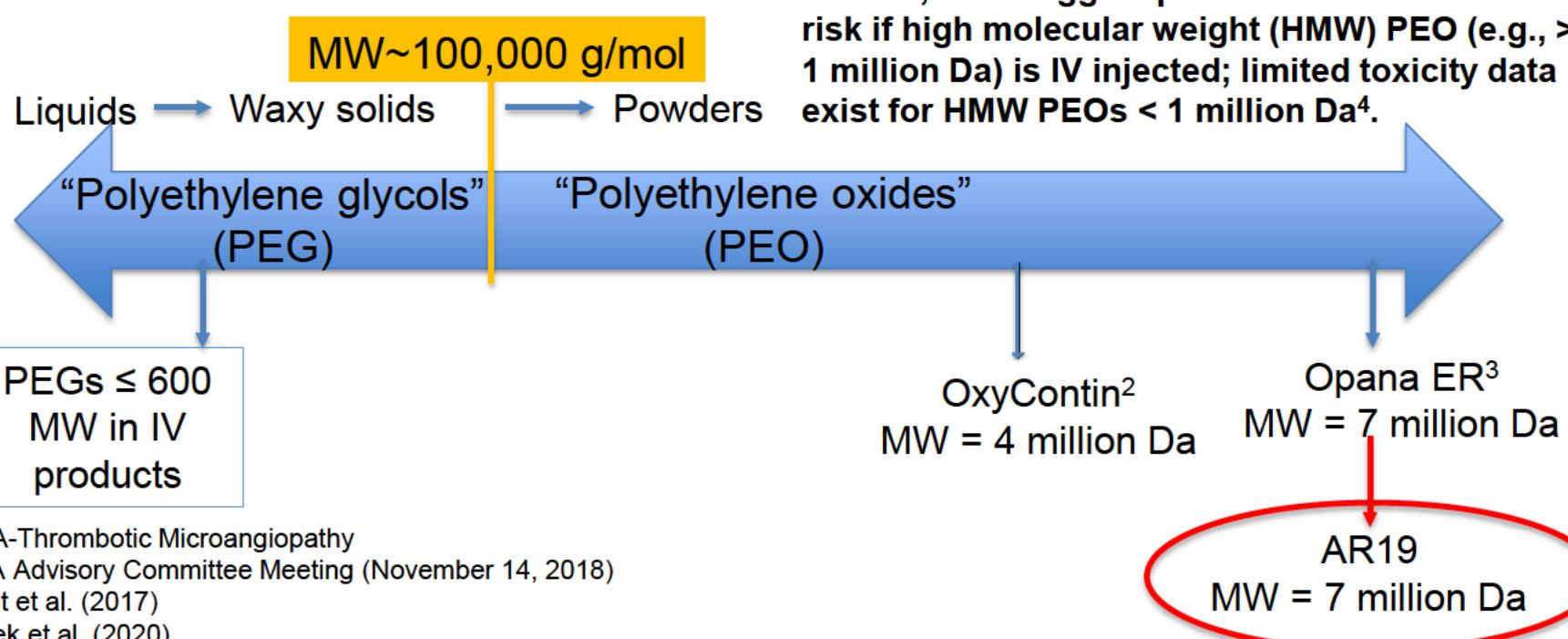
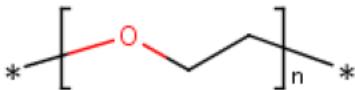
- The U.S. Food and Drug Administration (FDA) has no nonclinical safety concerns with AR19 excipients when the product is used as intended (oral).
- Two excipients specifically raise toxicity concerns if administered via unintended routes: Polyethylene Oxide 7 Million Daltons (Da) (PEO 7M Da) and talc.
- The Applicant provided data to assess the risks associated with the excipients when the product is misused via intravenous (IV) and intranasal (IN) routes.
- Under the conditions used, the data provided by the Applicant suggest that IV injection of one extract of AR19 did not result in clear evidence of thrombotic microangiopathy (TMA), as observed with reformulated Opana Extended Release (ER) (Hunt et al., 2017). However, there are limitations to these types of studies.
- **FDA cannot rule out the possibility that adverse effects could occur with drug product extracts following other manipulation methods or with more frequent and/or prolonged administration of manipulated AR19 for IV route.**

Safety Assessment of Excipients

FDA

- FDA has regulatory guidance for evaluating the safety of excipients for the intended route of administration and for the intended reformulations of oral products to IV drug products.
- FDA does not have a formal guidance document for evaluating the safety of oral drug products administered by the unintended routes of administration.
- Prompted by unanticipated outcomes that arose during postmarketing experience with reformulated Opana ER, FDA now evaluates the potential risk associated with excipients in abuse deterrent formulations (ADF) of opioids when the products are manipulated for misuse via alternative routes of administration.
- We employed a similar approach for this development program due to the potential for misuse of an ADF of amphetamine.

Polyethylene Oxide Polymers in Various ADFs



¹TMA-Thrombotic Microangiopathy

²FDA Advisory Committee Meeting (November 14, 2018)

³Hunt et al. (2017)

⁴Baek et al. (2020)

Postmarketing Clinical Experience with Opana ER Reformulation



Unanticipated outcomes with the introduction of reformulated Opana ER:

- Adverse events resulting from manipulation of the formulation for use by the unintended IV route of administration
 - Anemia, thrombocytopenia, TMA, acute kidney injury, retinal damage, and cardiac toxicity.

Published Nonclinical Investigations of Toxicities from Reformulated Opana ER



- Guinea pigs were injected with PEO 7M+ (PEO 7M Da plus other excipients) at doses that were predicted to mimic dosing in humans who manipulate Opana ER for IV use.
- Animals demonstrated anemia, TMA, and acute kidney injury consistent with human adverse events.
 - Not due to lack of blood compatibility directly, but likely indirect via increased sheer stress in microvasculature and deposition of free hemoglobin in tissues

Hunt et al. (2017) Blood 129(7): 896-905

Key Points to Consider Regarding Previously Approved of PEO-Containing Drugs

- Other FDA-approved opioid and stimulant products also contain PEO (e.g., OxyContin, Hysingla, Arymo, Zohydro, and Concerta)
 - To date, these products do not appear to carry same risk for TMA as reformulated Opana ER
 - Six published reports of TMA with IV OxyContin
- Not all PEO-based drug products are the same, differential risk could theoretically be based on:
 - Differences in manufacturing processes, curing methods, heat, additives, etc.
 - Differences in MW of PEO used
 - Differences in methods used to prepare these products for abuse via IV route
 - Differential patterns of abuse of the drug substances and/or drug products

APPLICANT'S APPROACH TO RISK CHARACTERIZATION OF AR19 EXCIPIENT, PEO 7M Da

Comparison of Category 1 Conditions Considered in the Toxicological Risk Assessment of AR19



Conditions**	Syringeable? (any temperature)	Injectable? (suitable physiological temperature)	Syringeable Amphetamine (mg) (%)	PEO > 1M Da (mg)
1	Yes	Yes	4.9 (12%)	1.25
2	Yes	Yes	11.2 (28%)	<3.90 [†]
3	Yes	No	16.8 (42%)	13.54
4	Yes	No	1.2 (3%)	<1.05 [†]
5	Yes	No	17.3 (43%)	‡
6	Yes	Yes	5.0 (13%)	<5.23 [†]
7	Yes	No	12.1 (30%)	1.58
8	Yes	Yes	20.1 (50%)	<1.55 [†]
9	Yes	Yes	11.1 (28%)	<3.45 [†]

- [†] Noted as below the limit of quantification in the Applicant's Advisory Committee Briefing Document.
- [‡] Mass of extract too small to be analyzed.
- **Extraction from a single 40 mg AR19 capsule.

In Vitro Hemolysis Study Results



Conditions**	Syringeable? (any temperature)	Injectable? (suitable physiological temperature)	Syringeable Amphetamine (mg) (%)	PEO > 1M Da (mg)
1	Yes	Yes	4.9 (12%)	1.25
2	Yes	Yes	11.2 (28%)	<3.90 [†]
3	Yes	No	16.8 (42%)	13.54
4	Yes	No	1.2 (3%)	<1.05 [†]
5	Yes	No	17.3 (43%)	‡
6	Yes	Yes	5.0 (13%)	<5.23 [†]
7	Yes	No	12.1 (30%)	1.58
8	Yes	Yes	20.1 (50%)	<1.55 [†]
9	Yes	Yes	11.1 (28%)	<3.45 [†]

- [†] Noted as below the limit of quantification in the Applicant's Advisory Committee Briefing Document.
 - [‡] Mass of extract too small to be analyzed.
 - *Compared with positive control in this study, PEO 8M Da.
 - **Extraction from a single 40 mg AR19 capsule.
- 15%* 11%* 14%*
- Hemolysis

Applicant's Basis for Selection of Condition for In Vivo Toxicological Testing



Conditions**	Syringeable? (any temperature)	Injectable? (suitable physiological temperature)	Syringeable Amphetamine (mg) (%)	PEO > 1M Da (mg)
1	Yes	Yes	4.9 (12%)	1.25
2	Yes	Yes	11.2 (28%)	<3.90 [†]
6	Yes	Yes	5.0 (13%)	<5.23 [†]
8	Yes	Yes	20.1 (50%)	<1.55 [†]
9	Yes	Yes	11.1 (28%)	<3.45 [†]

“Worst case” scenario with respect to injectable amphetamine

- ↑Amphetamine; ↓PEO
- No hemolysis in vitro.
- Used heat pre-treatment which degrades the PEO in the extract

• [†] Noted as below the limit of quantification in the Applicant's Advisory Committee Briefing Document.

• **Extraction from a single 40 mg AR19 capsule.

For in vivo toxicology studies, the Applicant utilized only extract from Condition 8.

In Vitro Hemolysis Study Results (Injectable Extracts)



Conditions**	Syringeable? (any temperature)	Injectable? (suitable physiological temperature)	Syringeable Amphetamine (mg) (%)	PEO > 1M Da (mg)
1	Yes	Yes	4.9 (12%)	1.25
2	Yes	Yes	11.2 (28%)	<3.90 [†]
6	Yes	Yes	5.0 (13%)	<5.23 [†]
8	Yes	Yes	20.1 (50%)	<1.55 [†]
9	Yes	Yes	11.1 (28%)	<3.45 [†]

Condition 1 is an extraction at room temperature and not heat pre-treated

- [†] Noted as below the limit of quantification in the Applicant's Advisory Committee Briefing Document.
- **Extraction from a single 40 mg AR19 capsule.

For in vivo toxicology studies, the Applicant utilized only extract from Condition 8.

Pivotal In Vivo Toxicology Study with AR19 Condition 8 Extract



- **Study No. LT30TD:** Rabbits (4/sex/group for main; 3/sex/group for recovery) were IV infused daily with either positive control or AR19 Condition 8 extract. Main group rabbits were sacrificed on Day 7 and recovery group rabbits were sacrificed on Day 21.
 - **Positive control:** unmanufactured PEO 7M Da (0.35 mg/kg/day; 0.75 mL/kg/min for 2 minutes)
 - **Premature death/euthanization of all positive control rabbits on Day 1.** Animals had clotted blood in the heart and major blood vessels. No histopathological changes.
 - **AR19 Condition 8 extract** (28.3, 56.6, and 84.9 mg/kg/day; 0.75 mL/kg/min for 2 minutes)
 - **No clear adverse effects**

No clear evidence of TMA or acute kidney injury from AR19 Condition 8 extract under the conditions tested in this study.

Limitations of Applicant's Approach to Risk Assessment for PEO 7M Da



- The full chemical content of the syringeable material tested in the AR19 IV toxicology study is not known (i.e., 14.97% unidentified impurities).
- Multiple conditions were injectable at physiological temperatures and yielded amphetamine but were not tested. Some of the injectable extracts yielding higher HMW PEO were not evaluated.
- Only assessed the one injectable extract which contained heat-pretreated PEO.
- Studies were limited in terms of duration of treatment and number of injections and dosing regimens tested are not expected to reflect all potential human patterns of abuse.

APPLICANT'S APPROACH RISK CHARACTERIZATION OF AR19 EXCIPIENT, TALC

Applicant's Approach for IV Risk Assessment of Excipient, Talc, in AR19

- Based on literature studies:
 - Talc exposure via IV and IN routes can cause well-known toxicities such as local tissue necrosis, granulomas, thrombosis, retinopathy, lung fibrosis, and talc-induced pneumonia.
 - We agree that existing Category 1 data indicate that small quantities of talc are present in syringeable and insufflatable material.
- However:
 - Talc could accumulate and cause chronic toxicities
 - We conclude that the risk from talc in AR19 is likely similar to manipulation of non-ADF formulations that contain talc.

Summary

- The data provided by the Applicant have limitations and do not alleviate FDA's concerns about the safety of the excipients in this product if administered via an unintended route (e.g., IV).
- If AR19 is manipulated in a manner that results in injectable HMW PEO administration, we cannot rule out the possibility of TMA.
- Talc exposure via injecting or snorting manipulated AR19 capsules likely poses a concern similar to other non-ADF oral formulations that contain talc.

