

FDA Briefing Document

Psychopharmacologic Drugs Advisory Committee and Drug Safety and Risk Management Advisory Committee Meeting

October 8, 2020

Topic: New Drug Application 211179

Immediate-Release Amphetamine Sulfate for the Treatment of
Attention Deficit Hyperactivity Disorder

The attached package contains background information prepared by the U.S. Food and Drug Administration (FDA) for the members of the Advisory Committee. The FDA background package typically contains assessments, conclusions, and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final positions of the individual reviewers, the Review Division, or the Office. FDA has brought New Drug Application 211179, immediate-release amphetamine sulfate for the treatment of attention deficit hyperactivity disorder, to this Advisory Committee to obtain the Committee's insights and opinions. The background package may not include all issues relevant to the final regulatory recommendation; instead, it focuses on issues identified by FDA for discussion by the Advisory Committee. FDA will not issue a final determination on the issues at hand until input from the Advisory Committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the Advisory Committee meeting.

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Glossary

AAPCC	American Association of Poison Control Centers
ADHD	attention deficit hyperactivity disorder
ADF	abuse-deterrent formulation
API	active pharmaceutical ingredient
AUC _{0-∞}	area under the curve from time zero to infinity
ASI-MV	Addiction Severity Index-Multimedia Version
CII	Schedule II
C _{max}	maximum concentration
CHAT	Comprehensive Health Assessment for Teens
CNS	central nervous system
CSS	Controlled Substance Staff
DIM	National data on Drug-involved Mortality
ED	emergency department
E _{max}	maximum effect
ER	extended-release
FAERS	FDA Adverse Event Reporting System
FDA	Food and Drug Administration
HAP	human abuse potential
HMW	high molecular weight
ICD-10	International Classification of Diseases, Tenth Edition
IN	intranasal
IND	investigational new drug
IR	immediate-release
IV	intravenous
LD	listed drug
M	million
MRHD	maximum recommended human dose
MTF	Monitoring the Future
NAVIPPRO	National Addictions Vigilance Intervention and Prevention Program
NDA	new drug application
NEIS-CADES	National Electronic Injury Surveillance System—Cooperative Adverse Drug Event Surveillance
NMU	nonmedical use
NPDS	National Poison Data System
NSDUH	National Survey on Drug Use and Health
NVSS-M	National Vital Statistics System-Multiple Causes of Death Database
OSE	Office of Surveillance and Epidemiology
ODT	orally disintegrating tablet
PCC	Poison Control Center
PDAC	Psychopharmacologic Drugs Advisory Committee
PEO	polyethylene oxide
PEG	polyethylene glycol
PMR	postmarketing requirement

REMS	risk evaluation and mitigation strategy
SUD	substance use disorder
TEDS	Treatment Episode Data Set
TMA	thrombotic microangiopathy
VAS	visual analog scale

1. DIVISION DIRECTOR MEMORANDUM

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: October 8, 2020

FROM: Tiffany R. Farchione, MD
Director (Acting)
Division of Psychiatry, Office of Neuroscience

TO: Members of the Psychopharmacologic Drugs Advisory Committee (PDAC) and Drug Safety and Risk Management (DSaRM) Advisory Committee

SUBJECT: October 8, 2020, Joint Meeting of the PDAC and DSaRM Advisory Committee

Arbor Pharmaceuticals, LLC (the Applicant) has submitted a new drug application (NDA) for AR19, amphetamine sulfate immediate-release (IR) oral capsules, for the treatment of attention deficit hyperactivity disorder (ADHD). This product has been formulated with properties intended to deter non-oral abuse. If language describing these properties is included in labeling, this product would be the first stimulant with such abuse-deterrent labeling.

Because there is no established pathway for developing abuse-deterrent stimulants, the Applicant has based their development program on the Food and Drug Administration's (the Agency) March 2016 guidance for industry, *General Principles for Evaluation of the Abuse Deterrence of Generic Solid Oral Opioid Drug Products*, and the April 2015 guidance for industry, *Abuse-Deterrent Opioids—Evaluation and Labeling*. The Agency has clearly communicated that the specific recommendations in its guidance documents apply to opioid drug products intended to be abuse-deterrent formulations (ADFs). The patterns of misuse and abuse, morbidity, and mortality associated with prescription stimulants are different from those associated with prescription opioids, and the Agency has not determined that prescription stimulant products warrant the same regulatory approach as opioid analgesics with regard to ADFs. The Agency has also expressed concerns that AR19 does not address the most frequent route of stimulant abuse (oral) and that the term *abuse deterrent* is often misinterpreted by the public (including prescribers) as indicating a lower risk of addiction.

AR19 is intended to deter abuse via the intranasal (IN) and intravenous (IV) routes. However, the IN human abuse potential (HAP) study did 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. Regarding IV abuse deterrence, syringeability studies showed that under certain extraction conditions, it was feasible to obtain a solution for injection containing at least 10 mg of amphetamine sulfate per mL of solution when using 20 mg and 40 mg AR19 capsules. Based on literature data, 10 mg of amphetamine administered in a small volume over a 60-second period would be the minimum reinforcing dose.

There are no nonclinical safety concerns with the proposed drug product formulation when used according to the indicated route of administration (oral). However, abuse-deterrent formulations are also evaluated for potential risk secondary to manipulation for use via unintended routes of administration (e.g., IN, IV). In this context, two excipients in this formulation present potential safety concerns: high-molecular-weight (HMW) polyethylene oxide (with a mass of 7 million Daltons; PEO 7M Da) and talc. IV injection of HMW PEO, such as PEO 7M Da, is associated with toxicities such as hemolysis and thrombotic microangiopathy (TMA) in guinea pigs and humans (CDC 2013; Hunt et al. 2017). IV and IN exposures to talc cause granulomas and pulmonary talcosis (an inflammatory reaction in the lungs that can lead to emphysema) (Hollinger 1990; Ward et al. 2000).

FDA recognizes that an ADF of a single product would likely have little impact on the overall problem of prescription stimulant nonmedical use (NMU; a concept that includes abuse and misuse), but it is also important to consider the broader question of whether effective ADFs of prescription stimulant products, in general, have the potential for public health benefit (i.e., for both patients and others in the household or community). Stimulants are widely prescribed, and their use is increasing. NMU of prescription stimulants is a serious public health concern, particularly for young adults (the demographic with the highest rates of prescription stimulant NMU). Risky use of other substances (i.e., polysubstance use) is also common among those who engage in NMU of prescription stimulants. Moderate to severe adverse medical outcomes as well as fatal overdoses do occur with NMU of prescription stimulants, often in the context of polysubstance use. Still, the overall magnitude of NMU of prescription stimulants has been stable over the last several years and is less prevalent than NMU of other drug classes such as prescription opioid analgesics. Although a substantial minority of prescription stimulant NMU occurs via snorting (insufflation) in the general population, most individuals who report non-oral NMU of prescription stimulants also report oral NMU. Some subpopulations more frequently report non-oral use of prescription stimulants, most notably individuals being assessed or treated for substance use disorders.

The potential broader public health impact of prescription stimulants that can deter non-oral routes of administration is unknown, considering the predominant route of NMU for these products being oral, the high prevalence of polysubstance use in people using prescription stimulants nonmedically, the availability of both pharmaceutical and illicit stimulant substitutes, and the potential for excipient harms. Section 9 of this briefing document describes postmarketing data on NMU of approved prescription stimulant products. These data are included to help inform the committees' consideration of whether AR19 or other prescription ADF stimulant products would be likely to have a meaningful benefit to patients or others who may access these products for NMU. FDA's experience with the postmarketing studies for ADF

opioid analgesics suggests some challenges we would also expect in attempting to assess ADF effectiveness and the broader public health effects of ADF stimulant products in real world settings. Challenges FDA noted at the recent [Advisory Committee meeting](#) discussing the results of postmarketing studies for OxyContin, an ADF extended-release oxycodone product, included the relatively low market penetration of ADF products; inherent limitations of the available data and observational study designs used to assess nonmedical use and associated adverse events; and the complex and evolving landscape of substance use in the United States, including growing polysubstance use and the increased availability and overdoses involving drugs such as illicitly-manufactured fentanyl and methamphetamine.

For approval of AR19, the Applicant is relying, in part, on the Agency's findings of safety and effectiveness for an approved IR amphetamine sulfate product. The Applicant has conducted a relative bioavailability study to establish a scientific bridge between AR19 and the approved product. Because the approved product is indicated only for pediatric patients, the Applicant conducted a clinical study in adult patients with ADHD to provide evidence of efficacy in the adult population in support of an expanded indication. The efficacy of AR19 for the treatment of ADHD is not a focus of this meeting. Rather, this meeting will focus on the product's proposed abuse-deterrent properties, whether the benefit:risk assessment for the drug supports approval of this new formulation, and the role of ADF stimulants more broadly in addressing the public health problem of stimulant NMU.

The following are points under consideration:

1. Considering the patterns of prescription stimulant nonmedical use in the United States, please discuss the potential public health impact of prescription stimulants formulated to be abuse-deterrent.
2. Based on the information provided, including the intranasal study comparing this product to amphetamine sulfate, has the Applicant provided adequate evidence that the formulation of AR19 would deter IN use?
3. Based on the information provided, including the syringeability study, has the Applicant provided adequate evidence that the formulation of AR19 would deter IV use?
4. Based on the information provided, has the Applicant adequately characterized the safety of AR19?
5. Discuss whether the benefits of AR19 outweigh the risks for the proposed indication.
6. What, if any, additional data are needed to address outstanding issues?

2. PURPOSE

The purpose of this meeting is to discuss NDA 211179 for amphetamine sulfate IR oral capsules, submitted by Arbor Pharmaceuticals, LLC, for the proposed indication of treatment of ADHD. The product has been formulated with properties intended to deter non-oral abuse, and the Applicant has submitted data to support such abuse-deterrant properties for this product. The Committees will be asked to discuss the overall risk-benefit profile of the product, including the potential public health impact, and whether the Applicant has demonstrated abuse-deterrant properties for their product sufficiently to support inclusion of language describing those properties in the labeling.

3. ATTENTION DEFICIT HYPERACTIVITY DISORDER

ADHD is a childhood-onset disorder characterized by inattentiveness, hyperactivity, or both. Treatment of ADHD may consist of pharmacotherapy, behavioral therapy, or their combination. Regardless of the approach used, treatment is recommended for all children with the diagnosis, because early treatment of ADHD leads to a better prognosis and fewer problems in adulthood (Sharma and Couture 2014). If left untreated, symptoms of ADHD may lead to emotional dysregulation, impaired social development, and academic underachievement. The estimated prevalence of adult ADHD is 4.4% (Kessler et al. 2006). Among patients with a substance-use disorder (SUD), 23% have comorbid ADHD ([van Emmerik-van Oortmerssen et al. 2012](#)).

Central nervous system (CNS) stimulants have been the mainstay of pharmacologic therapy for ADHD for half of a century. Most approved stimulants are formulations of methylphenidate or amphetamine. IR stimulants typically require dosing two- to three-times-daily, whereas extended-release (ER) formulations are administered once daily and have a duration of action up to 16 hours.

In the United States, ADHD-indicated stimulants (i.e., amphetamine and methylphenidate) are classified as Schedule II controlled substances: drugs having a currently accepted medical use, but with a high potential for abuse, and with use potentially leading to severe psychological or physical dependence.

4. TERMINOLOGY

In general, FDA has defined *misuse* as the intentional use, for *therapeutic* purposes, of a drug in a manner other than as prescribed or by an individual for whom it was not prescribed. FDA has defined *abuse* as the intentional, *nontherapeutic* use of a drug, even once, for its desirable psychological or physiological effects. In this document, some sections use the terms *misuse* and *abuse* based on these definitions, consistent with current labeling and regulatory language. However, it can be difficult to differentiate between *misuse* and *abuse* in epidemiologic data. Therefore, when discussing epidemiologic data, the term *nonmedical use* refers to both *misuse* and *abuse*.

We recognize that language can perpetuate stigma and negative bias toward individuals with SUDs and create barriers to effective treatment. For example, the term *abuse* has been identified as having a strong association with negative judgments and punishment. The term *abuse* is used in this document to describe a specific behavior that confers a risk of adverse health outcomes; it is not intended to imply moral judgment. FDA is committed to reducing stigma, expanding therapeutic options, and ensuring access to evidence-based treatment for individuals with SUDs.

We also recognize that the terms *abuse-deterrant formulation*, or *ADF* have been misunderstood to mean abuse- or addiction-proof formulations. The Agency is currently engaged in rigorous mixed-method, multi-phase research on healthcare providers' perspectives on issues related to ADFs and abuse-deterrance, including the terminology for describing these products.

5. RELEVANT REGULATORY HISTORY

5.1. Application-Specific History

5.1.1. June 14, 2016—Pre-IND Meeting

During this meeting, the Applicant outlined a plan to develop an IR amphetamine sulfate product with properties intended to deter abuse by the IN and IV routes. The Applicant stated an intent to develop this product via the 505(b)(2) regulatory pathway, relying in part on the Agency's previous findings of safety and effectiveness for Evekeo (amphetamine sulfate IR tablet, ANDA 200166, Arbor). Evekeo is approved for the treatment of ADHD in pediatric patients 6 years of age and older.

The Applicant described an intent to develop their product consistent with FDA's March 2016 guidance for industry, *General Principles for Evaluation of the Abuse Deterrence of Generic Solid Oral Opioid Drug Products*, and the April 2015 guidance, *Abuse-Deterrent Opioids—Evaluation and Labeling*. The Applicant initially planned to conduct only in vitro deterrence studies but was informed that HAP studies would be required.

5.1.2. March 30, 2017—Email Communication with Comments on Human Abuse Liability Study

The Agency provided feedback on the Applicant's proposed HAP protocol. Of note, the Agency advised the Applicant that the recommendations discussed in the *Abuse-Deterrent Opioids—Evaluation and Labeling* guidance for industry applied to opioid drug products intended to be abuse-deterrent formulations (ADFs). The Agency cautioned the Applicant that the responses to the Applicant's questions were based only on the scientific principles discussed in the guidance, with no implication that the regulatory approach to stimulant drug products intended to have abuse-deterrent properties would be identical to that for opioid ADF products. The comments regarding the applicability of the abuse-deterrent opioid guidance to the development of an abuse-deterrent stimulant were reiterated in our November 20, 2017, May Proceed letter following the Applicant's submission of the opening study under the Investigational New Drug (IND) application.

5.1.3. July 23, 2018—Pre-NDA Meeting

During a July 2, 2018, meeting with the Applicant for a related development program, the Agency communicated concerns about the Applicant's approach to ADF stimulant development; the Agency reiterated those concerns during this pre-NDA meeting. Specifically, the Agency provided the following overarching comments:¹

We remind you that the FDA's Guidance for Industry: Abuse-Deterrent Opioids—Evaluation and Labeling only applies to opioid drug products. Therefore, specific recommendations discussed in this guidance document for conducting Category 1, 2, and 3 studies also apply only to opioid drug products intended to be abuse deterrent formulations (ADFs). However,

¹ See 5.2 Additional Regulatory Context for an explanation of the categories of studies.

we will respond to your questions based on the scientific principles discussed in the Guidance, with no implication that FDA's regulatory decisions (e.g., regarding labeling) will be identical to the approach FDA has taken with ADF opioid analgesic products. The patterns of misuse and abuse, morbidity, and mortality associated with prescription stimulants are quite different from those associated with prescription opioids, and at this time FDA has not determined that prescription stimulant products warrant the same regulatory approach as opioid analgesics with regard to ADFs.

Moreover, it is important that an abuse-deterrent formulation affect relevant routes of abuse. In assessing the relevance of a route of abuse, we consider not only the prevalence (and relative prevalence) of abuse by that route, but also the magnitude of public health risks associated with abuse of the drug, both overall and by specific routes. It is up to sponsors to demonstrate how their product will impact each route of abuse and the health consequences associated with that route for a particular product. Your proposed formulation does not address abuse by the oral route, the most relevant route of stimulant abuse. Targeting the intranasal (IN) and intravenous (IV) routes of abuse for this product may have limited public health impact, even if Category 1-3 studies provide some support for AD properties by the IN or IV routes.

Thus, the performance of the IN-HAP study is of questionable value, as subjects will be exposed to the risks associated with the intake of the product intranasally, without necessarily providing a substantial benefit to patient safety or public health. We acknowledge that, in the past, we have not expressed concern regarding these HAP studies; however, our opinion in this matter has evolved due to our further and ongoing review of available evidence on this subject.

Although AR19 may deter intravenous and intranasal abuse when this formulation is used, there is no data that AR19 will reduce harm to those individuals who are currently abusing intravenous and intranasal stimulants. If prescribed this new formulation, those individuals may seek to satisfy their addiction in a less safe manner (i.e., with illicitly manufactured stimulants).

Your NDA submission should consider this impact on public health and explain how you will mitigate the potential for adverse effects to those already abusing stimulants. For example, prescriptions of AR19 could be restricted to newly diagnosed or stimulant naïve patients (who presumably are less likely to have already begun abusing stimulants). Established patients currently receiving amphetamine could also be prohibited from switching to AR19. The need for a Risk Evaluation and Mitigation Strategy (REMS) for this product will be informed by your discussion of these issues.

In addition, we are still concerned that a product associated with the phrase “abuse deterrent” is often misunderstood by the public as conferring less risk of dependence. Your NDA submission should address this concern.

The Applicant and Agency engaged in extensive discussion related to the comments above. The Applicant agreed to provide in the NDA a summary of the data supportive of a potential public health benefit of an ADF stimulant, and to propose an appropriate patient population.

The Agency also informed the Applicant that the nonclinical review of their application would focus on the safety of any unexpected and potential interactions between excipients, degradants, and impurities in the drug product formulation. Further, given that polyethylene oxide (PEO) is known to cause thrombotic microangiopathy when administered IV (Hunt et al. 2017) and talc causes granulomas with IN exposure and microemboli following intravenous use ([Hollinger 1990](#)), and given that this is an abuse-deterrent product, the use of PEO and talc as excipients in this drug product formulation regarding exposure in the population of stimulant abusers will remain a matter of review for the Controlled Substances Staff (CSS), clinical, and nonclinical.

5.1.4. January 15, 2019—Guidance Meeting

The Applicant requested this meeting to obtain the Agency’s opinion on an exploratory qualitative study in which they obtained feedback from healthcare providers about how to appropriately communicate the characteristics of AR19. The Applicant initiated this study in response to the Agency’s stated concern that the term *abuse deterrent* is often misunderstood. The Agency noted the limitations of the Applicant’s study and informed the Applicant that the Agency was engaged in rigorous mixed-method, multi-phase research on healthcare providers’ perspectives on issues related to ADFs and abuse-deterrence, including the terminology for describing these products (see page 24, Center for Drug Evaluation and Research: Drug Safety Priorities 2018²). The Applicant had intended to use the study to develop a pivotal descriptor labeling comprehension study, but instead opted to propose descriptive language in Section 9 (Drug Abuse and Dependence) of the planned AR19 label.

5.1.5. March 6, 2019—Written Responses Only Guidance

The Applicant requested the Agency’s guidance as to whether a toxicology study would be needed to further evaluate the AR19 formulation and its excipients. Based on extraction data provided by the Applicant, the Agency noted that the amount of HMW PEO extracted under certain conditions is approximately equivalent to that associated with toxicity in previous reports (Hunt et al. 2017). Based on this, it is reasonable to expect similar toxicities to that observed in published literature; therefore, the Agency advised against conducting an in vivo toxicology study because it was not expected to allay FDA concerns for the safety of the drug product formulation during misuse. The Agency also referred the Applicant to recent examples of potentially abuse-deterrent products that were withdrawn from the market or were not approved because of the presence of PEO.

² <https://www.fda.gov/media/124681/download>

5.1.6. March 29, 2019—Email Communication in Response to Written Responses Only Follow-up Questions

The Applicant indicated that they believe the HMW PEO extracted during manipulation of their product will have a molecular weight of less than 7M Da but acknowledged that the risks associated with PEO between 1M Da and 7M Da are unknown. They proposed an animal study to demonstrate the safety of the PEO extracted from their product.

The Agency advised the Applicant to characterize the PEO extracted from their product. The Agency offered advice on the design of an animal study that could provide insight into the potential risks of their product, provided that heating resulted in an extract free of 7M Da PEO.

5.2. Additional Regulatory Context

The Applicant is seeking approval and labeling of their product as an ADF. Currently, prescription opioid analgesics are the only drug class that contains products with descriptions of abuse-deterrent properties in labeling (i.e., that they are expected to deter abuse via certain routes of administration, including chewing, snorting, and injection). Two approved stimulants (Vyvanse and Concerta) have HAP study results in labeling that report a comparison to the abuse potential of other approved stimulant products; neither is considered to be an ADF.

In April 2015, FDA issued the final guidance for industry, *Abuse-Deterrent Opioids—Evaluation and Labeling*,³ outlining the Agency’s current thinking on the studies that should be conducted to demonstrate that a given opioid formulation has abuse-deterrent properties. The Guidance outlines several principles for evaluating the abuse-deterrent characteristics of an opioid formulation. First, studies should be scientifically rigorous, incorporate appropriate comparators and endpoints, and should take into consideration the known routes of abuse and whether the deterrent effects can be expected to have a meaningful impact on specific routes as well as the overall abuse of the product. The Guidance describes four categories of studies to evaluate the abuse-deterrent characteristics of an opioid formulation:

- Category 1: Laboratory-based in vitro manipulation and extraction studies
- Category 2: Pharmacokinetic studies
- Category 3: Clinical abuse potential studies (i.e., “drug liking” studies)
- Category 4: Postmarketing studies (i.e., epidemiologic studies)

The Guidance states that the goal of postmarketing (Category 4) studies is to determine whether the marketing of a product with abuse-deterrent properties results in meaningful reductions in abuse, misuse, and related adverse clinical outcomes (including addiction, overdose, and death) in the post-approval setting. It also notes that because the science of abuse-deterrence is relatively new and methods for evaluating the technologies used are evolving, FDA intends to take a flexible, adaptive approach to the evaluation and labeling of potentially abuse-deterrent products. The Agency also stated that because of the evolving nature of this field, no absolute magnitude of effect for establishing abuse-deterrence could be set, and that it intended to

³ <https://www.fda.gov/media/84819/download>

consider the totality of evidence when reviewing the results of studies evaluating abuse-deterrence.

Applicants for abuse-deterrent opioid analgesic products must conduct observational postmarketing studies to assess whether the properties intended to deter abuse resulted in meaningful decreases in abuse and related consequences in the postapproval setting. To date, only OxyContin has had sufficient market uptake to assess the impact of the formulation in the post-approval setting. The results of those postmarketing requirement (PMR) studies were discussed at an Agency Advisory Committee meeting held on September 10 and 11, 2020.⁴ The committee members were asked to discuss whether the PMR studies, in concert with other information from the published literature, demonstrated that reformulated OxyContin resulted in a meaningful reduction in abuse and overdose associated with the product. The committee members were also asked to discuss the broader public health impact of OxyContin's reformulation. The postmarketing experience with OxyContin may provide insight into the potential public health risks and benefits and relevant postmarketing questions for an ADF prescription stimulant product.

Public Health Risks and Benefits

Benefit-risk assessment is a foundation for FDA's regulatory review of all human drugs and biologics. In general, FDA considers the benefits and risks to the patient when the drug is used as labeled. Additionally, FDA has explicitly stated in a recent draft Guidance to Industry that, for regulatory decisions regarding opioid analgesics, we also consider the broader public health risks of the drug related to misuse, abuse, opioid use disorder, accidental exposure, and overdose in both patients and others, as well as any properties of the drug that may mitigate such risks.⁵ This patient and public health risk-benefit framework is also useful, however, for considering the potential impact of ADF stimulants.

Using this broader public health focus, FDA considers different populations who may be affected by the regulated product or by FDA's decision-making regarding that product. Here, the term "population" means a set of individuals defined in general terms by their therapeutic need for the prescription stimulant and their stimulant use behaviors. ***It is important to note that individuals may simultaneously fit into multiple populations and may move in and out of populations depending on their current situation.*** This characterization of populations, however, can be useful in considering the different benefits and risks of ADF stimulants, including unintended impacts in different groups. Broadly speaking, three important populations may be particularly relevant:

- *Individuals who require prescriptions stimulants for the treatment of ADHD, under the care of a healthcare provider (i.e., the intended population).* Importantly, these individuals may simultaneously fit into another category described below. A central goal for this population is availability of safe and effective therapies to manage their medical needs while minimizing the risks of misuse and abuse, addiction, and overdose. A potential safety

⁴ Meeting materials 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>

⁵ <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/opioid-analgesic-drugs-considerations-benefit-risk-assessment-framework-guidance-industry>

benefit of ADF stimulants related specifically to this population is a reduction in medication errors related to crushing extended-release formulations. However, unintended adverse effects from added excipients must be considered.

- *Individuals who nonmedically use prescription stimulants but do not regularly manipulate these products for use by routes (e.g., snorting, injecting, smoking) other than the intended route.* These individuals may obtain stimulants from their own prescription or from other sources and are at risk of harms from oral NMU as well as transitioning to non-oral use and the harms associated with these behaviors. These individuals may also engage in risky use of alcohol, other pharmaceuticals, or illicit substances. Important goals for this population are to reduce harms associated with NMU of prescription stimulants, including harms associated with the transition to manipulation and non-oral use (e.g., infectious complications of injection), and risk of progression to more severe stages of a SUD, overdose, and death.
- *Individuals who regularly manipulate prescription stimulants for use by routes (e.g., snorting, injecting, smoking) other than the intended route.* These behaviors may be associated with a more severe SUD, and these individuals may be more likely to engage regularly in polysubstance use, including risky alcohol use, NMU of other pharmaceuticals, and use of other illicit substances. A key goal related to this population is to reduce the likelihood and frequency of risky behaviors and adverse outcomes (e.g., injection-related harms, overdose) associated with these behaviors, but we must also consider unintended effects of shifts to use of more dangerous substances, such as illicit methamphetamine.

In September 2019, the Agency issued a Federal Register Notice⁶ seeking comments from interested parties—including patients, patient advocates, healthcare providers, academics, researchers, the pharmaceutical industry, and other government entities—on considerations related to the development and evaluation of ADFs of CNS stimulants and whether such products could play a role in addressing public health concerns related to prescription stimulant misuse and abuse. A total of 1,382 comments were submitted, with the majority (about 90%) from patients and individual consumers. Approximately 3% of the comments came from academia and 2% from consumer groups; two medical associations also provided comments. An assessment of the comments by an independent consulting firm found that the vast majority of comments (approximately 96%) across all questions were negative (i.e., expressed negativity towards the development of ADFs, additional regulations as a result of ADFs, or concerns regarding treatment).

⁶ <https://www.regulations.gov/docket?D=FDA-2019-N-3403>

6. SUMMARY OF CLINICAL DATA

AR19 is an IR capsule formulation of amphetamine sulfate. The proposed dose strengths are 2.5, 5, 10, 15, 30, and 40 mg. The maximum recommended daily dose is 40 mg. AR19 is to be administered once in the morning followed by a second dose 4 to 6 hours later (e.g., 20 mg twice per day).

The Applicant is relying, in part, on the Agency's findings of safety and effectiveness for the listed drug (LD), Lannett's amphetamine sulfate tablets (ANDA 083901). Lannett's ANDA is listed in the Discontinued Product List section of Approved Drug Products with Therapeutic Equivalence Evaluations (Orange Book). FDA has determined that the Lannett amphetamine sulfate tablets 5 and 10 mg were not withdrawn from sale for reasons of safety or effectiveness. The reference standard is Evekeo tablets (amphetamine sulfate tablets, Arbor, ANDA 200166). Lannett's amphetamine sulfate tablet ANDA is approved for the treatment of ADHD in pediatric patients (3 to 17 years). The Applicant established a scientific bridge to Lannett's ANDA 083901 via a two-treatment, two-period, two-way crossover relative bioavailability study comparing AR19 to Evekeo ANDA 200166, the reference standard, in 36 healthy adults. Because Lannett's indication does not include the adult population, the Applicant also conducted a 6-week, randomized, fixed-dose, double-blind, multicenter safety and efficacy study of AR19 in adults with ADHD ages 18 to 55 years. The adult clinical study was successful and is considered sufficient for extending the indicated population to adults if this product is approved.

7. FINDINGS ON ABUSE-DETERRENT PROPERTIES OF AR19

The proposed formulation, AR19, is an IR capsule formulation that contains pellets of racemic amphetamine as the sulfate salt. The drug product is to be administered orally or by opening the capsules and sprinkling the pellets over food for subsequent ingestion with the food. The formulation is designed to resist the manipulation required for IN, smoking, and IV use. Note that the drug product was not intended to—and does not—deter misuse or abuse by the oral route.

The formulation was developed by adapting the INTAC abuse-resistance technology, which was previously used in the manufacture of Opana ER tablets. The deterrent properties of the drug product are imparted by excipients, which provide resistance to crushing and can result in solutions that become viscous hydrogels when exposed to water. These excipients are PEO and polyethylene glycol (PEG). Three batches of pellets (low, middle, and high PEO and PEG contents) are used—the particular batch used depends on the dosage strength of the capsule. The 2.5- and 5-mg strengths contain a *common pellet batch* of a high percentage per weight per capsule of PEO and PEG; the 10-, 15-, and 20-mg strengths contain a *common pellet batch* of a middle percentage per weight per capsule of these excipients; and the 30- and 40-mg strengths a *common pellet batch* of a low percentage per weight per capsule of these excipients.

The development of abuse-deterrent IR formulations (either opioid or stimulant) is challenging, because the active pharmaceutical ingredient (API) must be rapidly bioavailable via the oral route. Therefore, regardless of any abuse-deterrent effects by the IV or IN routes, an IR product with physicochemical abuse-deterrent features is not expected to deter oral abuse. This is in contrast to extended-release (ER) opioid analgesic formulations, where those formulations are not expected to release the API all at once (i.e., dose dumping) upon manipulation, which may or may not result in an abuse-deterrent claim for the oral route but would regardless potentially avoid the serious safety issues associated with this release. Therefore, for an IR formulation, an abuse-deterrent claim for the IV or IN route must be weighed against the fact that the product can still be easily abused orally. It is important to note that abuse-deterrent formulations are not abuse-proof and can be abused by all routes, regardless of any abuse-deterrent effects.

The Applicant conducted premarketing studies to characterize the abuse-deterrent properties of the formulation, as described in the FDA guidance for industry, *Abuse Deterrent Opioids—Evaluation and Labeling*.⁷ However, although the scientific principles behind manipulation techniques may apply to the development of abuse-deterrent stimulants, the clinical relevance of the findings are less well understood than for the opioid class. When interpreting in vitro and HAP data for opioid abuse-deterrent formulations, we have learned that differences in the oral bioavailability of the API will determine the preferred routes of abuse and that intrinsic differences among APIs may exist; these lead to different abuse methods among the APIs based on reinforcing properties (e.g., drug liking).

⁷ FDA/CDER. Final guidance for industry, *Abuse Deterrent Opioids—Evaluation and Labeling*, 2015
<https://www.fda.gov/media/84819/download>

According to the guidance mentioned above, the Applicant conducted premarketing studies consisting of in vitro manipulation and extraction studies (Category 1), pharmacokinetic studies (Category 2), and an intranasal human abuse potential study (Category 3).

In vitro studies were conducted to evaluate the ease with which the formulation could be physically manipulated to reduce it to a powder that could be insufflated. Additional studies explored the feasibility of obtaining a solution for injection (syringeability studies) using the AR19 granules. Vaporization studies were conducted; however, these were not considered in the evaluation of the deterrent properties of the formulation because prescription amphetamine drug products are not significantly abused by smoking.

The in vitro studies employed representative samples of the highest strength of each of the three *common pellet batches* described above (5-, 20-, and 40-mg strengths). These studies were designed to assess the optimum conditions to defeat the formulation using a wide range of chemical and physical conditions, temperatures, and durations. The comparator in these studies was a commercially available IR (\pm)-amphetamine sulfate product, Evekeo 10-mg tablets.

The Applicant also conducted a HAP study to evaluate the abuse potential of manipulated AR19 compared to amphetamine sulfate API and placebo when administered IN to nondependent individuals who recreationally use stimulants IN.

In the following sections, we discuss the results of in vitro studies of the properties of AR19 when manipulated for purposes of preparing a sample for IV, IN, or inhalation (by smoking) administration. We also discuss relevant information on a dose of racemic amphetamine likely to be reinforcing when injected. Lastly, we summarize the findings of the HAP Study AR19.001, conducted to evaluate the abuse-deterrent properties of AR19 by the IN route as measured by the subjective responses of subjects on Drug Liking and other similar endpoints following IN administration of manipulated AR19, amphetamine (positive control), or placebo.

7.1. Category 1 Studies: Evaluation of In Vitro Studies

Multiple in vitro abuse-deterrent studies were conducted to assess the relative difficulty and effectiveness of various potential manipulation methods to defeat the drug product's abuse-deterrent properties. Only the methodologies that reflect the most probable abuse approaches and that pose the most challenges to the drug product under evaluation are summarized below. When used, the comparator is an FDA-approved amphetamine sulfate IR tablet (10 mg) or amphetamine sulfate API.

7.1.1. Physical Manipulation (Particle Size Reduction)

Several simulated common techniques that are used to manipulate the proposed drug product (5 mg, 20 mg, and 40 mg) and the comparator (10 mg) were studied. Selected readily available physical manipulation tools representative of cutting, crushing, and grinding mechanisms were employed to reduce particle size. The particle-size distribution of powders was measured after physical manipulation. Not all tools were equally successful in reducing the particle size of the drug product. However, particle size reduction using a manual tool resulted in sixty-nine to seventy-six percent of particles <500 microns for the drug product and approximately ninety-

eight percent of particles <500 microns for the comparator product (10 mg). Pretreatment of samples did not significantly influence the particle size. The measurement of 500 microns is specifically mentioned because particles of roughly this size are insufflatable.

7.1.2. Large Volume Extraction Studies

Large volume extraction studies evaluated the ability to produce a drinkable solution of drug product with a high amount of extracted drug substance (amphetamine sulfate). Extracting amphetamine sulfate from AR19 capsule contents using large volumes yielded close to 100% of the amphetamine sulphate. Similar results were observed with the comparator product (10 mg).

7.1.3. Small and Large Volume Extractability and Syringeability Studies

Small volume extractions, using <10 mL, were conducted to assess the potential for syringeability and injectability of the manipulated drug product (5, 20, and 40 mg). Testing included pretreated/non-pretreated and intact/manipulated capsule contents extracted in solvents at room temperature and elevated temperature. Multiple solvents as well as a variety of extraction times were tested. Conditions were confirmed in which up to 50.2% (approximately 20 mg from a 40-mg capsule and approximately 10 mg from a 20-mg capsule) of amphetamine sulfate could be isolated and potentially injected using a 23-gauge needle. Other conditions did not isolate more than 45% of the amphetamine sulfate present in a capsule. It was not feasible to extract amphetamine sulfate from multiple capsules simultaneously.

Large volume extractions, using ≥10 mL, followed by volume reduction (e.g., boiling) to an injectable amount were conducted to assess the potential syringeability and injectability of the manipulated product (5, 20, and 40 mg). Testing included pretreated/non-pretreated and intact/manipulated drug product extracted in solvents at room temperature and elevated temperature. Multiple solvents as well as varying extraction times were tested. Conditions were confirmed under which up to 31.5% (15.75 mg) of amphetamine sulfate present in a single 40-mg capsule could be isolated and potentially injected using a 23-gauge needle. Other conditions could not isolate more than 25.9% of the amphetamine sulfate present in a capsule.

Interpretation of the in vitro syringeability studies with respect to an abuse-deterrent effect via the IV route requires an understanding of the dose-response curve for IV (\pm)-amphetamine sulfate in HAP studies.

The Applicant did not conduct a pilot study to determine what would constitute a reinforcing IV dose of (\pm)amphetamine sulfate when rapidly IV injected over a 30-to-60-second period, which would constitute a reasonable injection time based on reports of people who inject drugs (Zernig et al. 2003). When assessing the subjective effects of IV-administered drugs, the rate of injection and the dose injected are equally relevant (de Wit, Bodker et al. 1992, Comer, Ashworth et al. 2009).

Fischman et al. demonstrated that 10 mg of dextroamphetamine, administered intravenously in a 1 mL volume over 60 seconds to volunteers with a long history of illicit intravenous cocaine abuse, produced similar subjective effects to 16 mg of intravenous cocaine, as measured using the Addiction Research Center Inventory stimulant subscale. It also produced similar changes in

the mood clusters of friendliness, amphetamine-like feelings, and vigor to 8 mg of cocaine ([Fischman et al. 1976](#)). The main limitation of this study is that only the 10 mg dose of dextroamphetamine was tested, and that dextroamphetamine has been described as the more psychoactive of the two isomers of amphetamine (levoamphetamine and dextroamphetamine) ([Balster and Schuster 1973](#)). However, no data on the reinforcing properties of administration of the racemic mixture were found, preventing evaluation of the contribution to cardiovascular effects of the less psychoactive but more potent enantiomer.⁸ Although the dextroamphetamine component is known to be more potent for psychoactive effects, it is unknown how much the stronger cardiovascular effects (i.e., sympathomimetic) attributable to the levoamphetamine component contributes to the overall positive experience in an abuse setting. Therefore, we determined that a reasonable minimum reinforcing dose would be 10 mg of amphetamine administered IV in a small volume over a 60-second period, based on the available literature.

7.1.4. Smoking

The smokeability of amphetamine sulfate drug substance, manipulated comparator (10 mg), and manipulated drug product (5, 20, and 40 mg) was assessed using a smoking simulation device. Between 33% and 49% of amphetamine sulfate drug substance was volatilized using a smoking simulation device. Small quantities of amphetamine sulfate were volatilized from manipulated comparator (approximately 2.5%) and manipulated drug product (2 to 10%).

However, as summarized above, vaporization studies were not considered in the evaluation of the deterrent properties of this formulation because prescription amphetamine drug products are not known to be significantly abused by the smoking route.

7.2. Category 2 and 3 Studies: Pharmacokinetics and Intranasal Human Abuse Potential

The Applicant conducted a HAP study to evaluate the deterrent properties of AR19 when administered IN.

7.2.1. Study AR19.001

Study Title: A Randomized, Double-Blind, Active- and Placebo-Controlled, Three-Way Crossover Study to Determine the Abuse Potential of Manipulated AR19 (Amphetamine Sulfate) Compared to Amphetamine Sulfate API and Placebo When Administered Intranasally to Nondependent Recreational Stimulant Users

This was a randomized, double-blind, active- and placebo-controlled, two-part (A and B) study to evaluate the IN abuse-deterrent effects of AR19 pellets compared with amphetamine API when administered to nondependent individuals who recreationally use stimulants. A dose selection phase was included in the study design to identify a dose of IN amphetamine sulfate that was well-tolerated and showed clear discrimination from placebo on subjective

⁸ Arbor (2019). “Arbor Pharms LLC, product label, Evekeo 20 mg ODT, NDA 209905.” Access at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/209905s000lbl.pdf.

pharmacodynamic (PD) measures. The dose identified was subsequently used in the qualification and treatment phases.

Primary Objective

The primary objective was to evaluate the abuse potential of manipulated AR19 compared to amphetamine sulfate API and placebo when administered IN to nondependent individuals who recreationally use stimulants.

Secondary Objectives

The secondary objectives of the study were:

- To evaluate the PK profile of manipulated AR19 compared to amphetamine sulfate API when administered IN.
- To evaluate the safety and tolerability of manipulated AR19 compared to amphetamine sulfate API and placebo when administered IN.

Inclusion Criteria

- Current use of stimulants in individuals who had used stimulants for recreational (nontherapeutic) purposes (i.e., for psychoactive effects) at least 10 times in their lifetime and at least 1 time in the 12 weeks before screening.
- Must have had experience with IN drug use for recreational (nontherapeutic) purposes on at least three occasions in the year prior to screening.

Part A—Dose Selection

Given that the PD effects of IN-administered amphetamine sulfate are unclear, the first part of this study (Part A) was a dose-selection phase to identify an appropriate IN dose of amphetamine sulfate API that would be well-tolerated and produce robust responses on PD measures in the main study (Part B).

Part A evaluated amphetamine API at three dose levels: 20, 30, and 40 mg. Based on the PD results, the absence of treatment-related and moderate-to-severe adverse events (AEs), and the fact that subjects were able to completely insufflate the dose, amphetamine API 40 mg was selected for use in the qualification and treatment phases.

Part B

The Part B qualification phase was a randomized, double-blind, two-way crossover, drug discrimination test to identify subjects able to sensitively discriminate between the active control (amphetamine sulfate API powder) and placebo powder. Subjects received single IN doses of amphetamine sulfate API or placebo. Subjects had to meet the following qualification phase criteria to be eligible to enter the treatment phase:

1. Peak Drug Liking visual analog score of at least 75 points in response to amphetamine sulfate API and greater than that of placebo (a difference of at least 15 points).

2. A placebo response based on a Drug Liking score of 40 to 60 points (inclusive).

The treatment phase used a randomized, double-blind, active- and placebo-controlled, three-way crossover design to evaluate the IN abuse potential of manipulated AR19. Both AR19 and placebo pellets were manipulated to reduce the particle sizes for insufflation. The method that the Applicant identified in the in vitro studies that effectively reduced the pellets to a fine consistency (<500 µm) suitable for insufflation was chosen to manipulate the sample in the human abuse potential study. Amphetamine sulfate API powder was selected as the active comparator.

Drug Treatments and Administration

In the main study, subjects received each treatment in amber-colored vials to mask the differences in their weight and appearance. In the qualification phase, subjects received single doses of 40 mg of amphetamine API and 40 mg of microcrystalline cellulose as placebo. During the treatment phase, subjects received single IN doses of each of the following treatments in a randomized, double-blind fashion:

- Treatment A—Placebo: This treatment consisted of microcrystalline cellulose matched to the weight of the amphetamine API and a second placebo matched to the weight of the AR19 test sample.
- Treatment B—Amphetamine sulfate API: This treatment consisted of 40 mg of amphetamine API and AR19 placebo powder (291 mg).
- Treatment C—Manipulated AR19 (40 mg capsule): This treatment consisted of manipulated AR19 (capsule contents weighing 291 mg) and amphetamine API placebo powder (40 mg).

Visual Analog Scales

PD assessments were performed using a unipolar or bipolar VAS. Each VAS was scored from 0 to 100. Unipolar VASs were presented with anchors such as “not at all” (score=0) to “extremely” (score=100), where the neutral point equaled 0 (High VAS). Bipolar VASs were administered such that the neutral point equaled 50 (Drug Liking, Overall Drug Liking, Take Drug Again). The neutral point was labeled with an anchor, such as “neither like nor dislike.”

Primary Endpoint

- The maximum (peak) effect (i.e., E_{max}) for Drug Liking (“at this moment”), assessed on a bipolar (0–100 point) VAS.

Secondary Endpoints

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

Statistical Analysis: The Applicant conducted two types of analyses on the above endpoints, one being a difference in means between groups and the other a responder analysis.

Regarding the first group of analyses, the study was not designed simply to detect a difference in means between treatment groups. Instead, the Applicant designed the study so that the difference in means on the prespecified endpoints would have to meet a threshold of ***at least a 10%*** reduction with manipulated AR19 as compared to amphetamine 40 mg in order for this finding to be considered statistically significant.

The responder analysis was designed to determine if greater than 50% of subjects were responders, where responders were defined as those subjects having at least a 10% reduction on the prespecified endpoints.

Pharmacokinetic Results

Following IN administration, manipulated AR19 capsules (40 mg) showed lower systemic exposures (30% lower maximum concentration (C_{max}) and 20% lower area under the curve from time zero to infinity ($AUC_{0-\infty}$)) compared to amphetamine sulfate API powder (active control; 40 mg).

A cross-study comparison (between this HAP study and AR19.005, an oral PK study) of IN administration of amphetamine sulfate API powder (40 mg) and oral administration of AR19 capsules (40 mg) showed that systemic exposures to l-amphetamine and d-amphetamine after IN administration are lower (40% lower C_{max} and 30 to 40% lower $AUC_{0-\infty}$) than those of oral administration. Furthermore, when compared to oral administration of AR19 capsules, IN administration of manipulated AR19 capsules showed lower systemic exposures (60% lower C_{max} and 40% to 50% lower $AUC_{0-\infty}$) to l-amphetamine and d-amphetamine.

These data demonstrate that, in general, IN administration of amphetamine results in lower systemic exposures to l- and d-amphetamine as compared to oral administration and that this phenomenon is more pronounced with IN administration of manipulated AR19 capsules.

Pharmacodynamic Results

Of the 40 subjects randomized in the treatment phase, 37 subjects completed all treatment periods, each of whom received a single IN dose of amphetamine API 40 mg, AR19 40 mg, or placebo (Completers Population). Validation of each measure (Drug Liking VAS, Take Drug Again, Overall Drug Liking, and High) was established by comparing the scores obtained for the API 40 mg treatment arm to those of placebo.

The Applicant stated that the planned statistical analysis of the difference between the mean Drug Liking E_{max} for amphetamine API 40 mg versus the mean value for placebo did not reach statistical significance at the prespecified alpha level of 0.025. Thus, the Applicant acknowledged that the study was not validated. In some instances, prespecified criteria can be used to remove subjects who did not provide reliable responses for the purpose of validating such a study. However, in this case, the Applicant did not prespecify any criteria for this purpose. As part of the analysis submitted in the NDA, the Applicant determined that one subject (Subject (b) (6)) was a likely contributing factor to the study not being validated. Thus, the Applicant conducted a post-hoc sensitivity analysis on the primary PD endpoint to identify and exclude outliers and undertook a formal outlier analysis to identify all subjects with outlier data points.

That analysis identified that “subject (b) (6) was shown to be the only subject in the Completers Population who scored 100 points for placebo and 50 points for amphetamine API 40 mg on Drug Liking VAS. PD data from Subject (b) (6) were determined to have substantially influenced the study results and were excluded from the evaluation of the study hypotheses.”

Given that the Applicant did not prespecify criteria for identifying and removing outliers, the resulting analyses should be considered exploratory, and statistical significance for all comparisons is nominal only.

Table 1 summarizes the results from the primary analysis on Drug Liking E_{max} for the Completers Population. The p-value for the comparison of amphetamine 40 mg and placebo, using a margin of 15 on the VAS, was greater than 0.025. This indicates that the validation test of the study failed because the positive control was not distinguishable from placebo.

Table 1. Primary Analysis Results on Drug Liking E_{max} (N=37)

Comparison	Med Diff	IQR	Test Value	p-Value	95% CI	
					LCL	UCL
Am40-P	23.0	11, 37	15	0.0877	13.1	32.0

Source: Division of Biometrics VI, FDA

AM40 = amphetamine 40 mg, CI = confidence interval, E_{max} = maximum effect, IQR = interquartile range, LCL = lower confidence limit, Med Diff = median difference, P = placebo, UCL = upper confidence limit

The Applicant conducted an analysis of the Completers Population excluding Subject (b) (6) and submitted it as part of the NDA. However, the p-value for the comparison of amphetamine 40 mg and placebo remained greater than 0.025—indicating that the validation test of the study failed. The Applicant indicated in the NDA that the study was valid after excluding Subject (b) (6); however, the Division of Biometrics VI did not agree with the Applicant’s analysis because of differences in opinion regarding the normality assumption.

The Agency conducted a modified completer analysis, which excluded subjects with unreliable responses based on what would have been acceptable prespecified criteria. For the Drug Liking scale, the following elimination criteria were used in defining the modified completer population:

1. Similar E_{max} scores (within a 5-point difference) from a subject across all study treatments (including placebo)

OR

2. $E_{max}(\text{placebo}) > 60$
AND
 $E_{max}(\text{placebo}) - E_{max}(\text{positive control}) - 5 \geq 0$.

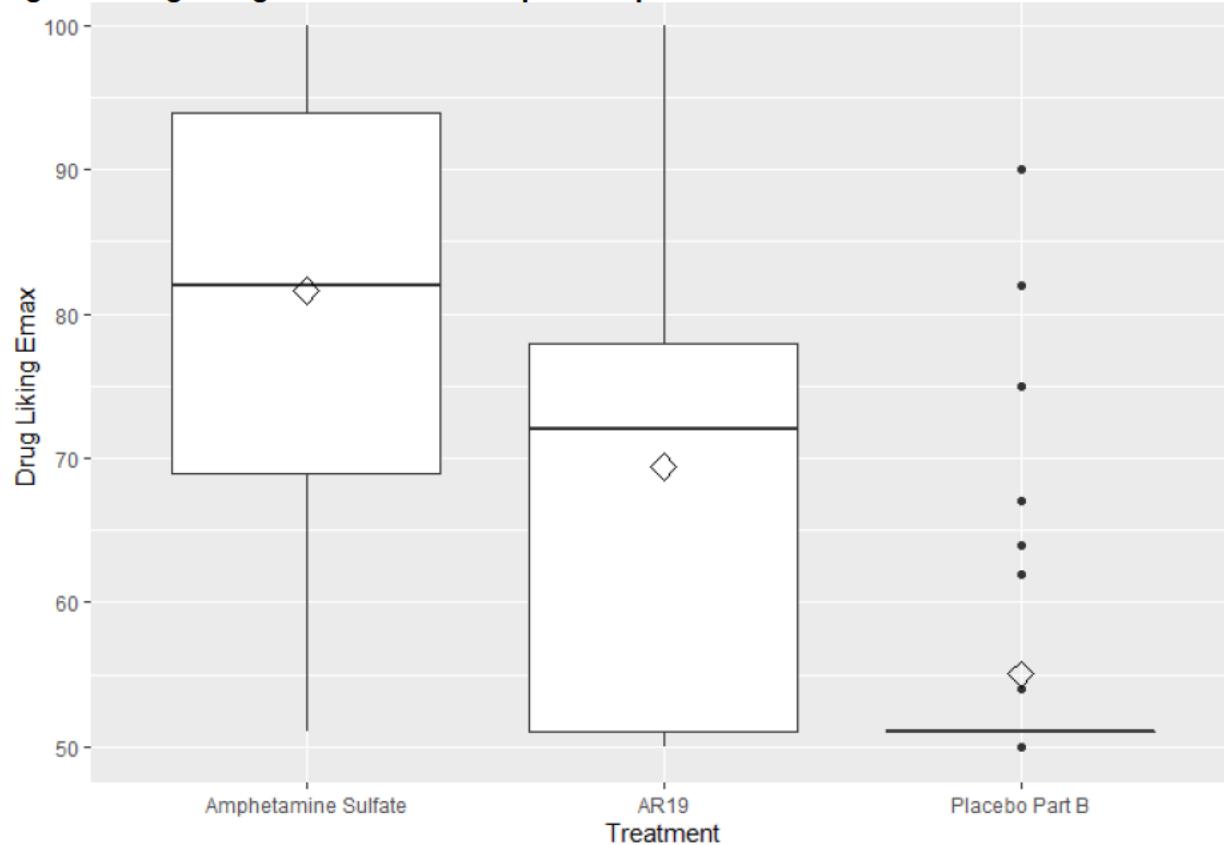
Four subjects met these criteria and were excluded to form the modified completer population (n=33), which was used for the following further post-hoc exploratory analyses:

1. Primary analysis and responder analysis for the primary endpoint.

2. Secondary analysis and responder analysis for the secondary endpoints.

[Figure 1](#) displays a boxplot of the Drug Liking E_{max} for the modified completer population.

Figure 1. Drug Liking E_{max} : Modified Completer Population



Lower edge of the box, Q1; higher edge of the box, Q3; line in the middle of the box, median; rhomboid point, mean

Source: Division of Biometrics VI, FDA

Abbreviation: E_{max} = maximum effect

[Table 2](#) summarizes the results from the primary analysis of the modified completer population.

Table 2. Primary Analysis Results: Drug Liking E_{max} 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

Source: Division of Biometrics VI, FDA

Abbreviations: E_{max} = maximum effect, LSMean = least square mean, SE = standard error, TRT = treatment

The Agency's analysis of the modified completer population showed that for Drug Liking, E_{max} (primary endpoint):

- The differences in means between the amphetamine 40 mg and placebo groups reached nominal statistical significance in this post-hoc analysis (i.e., greater than 15 points, with a p-

value of 0.0066), indicating this population (excluding outliers) would have led to a valid study.

- The differences in means of maximum Drug Liking between manipulated AR19 and amphetamine 40 mg did **not** reach nominal statistical significance using a minimum 10% margin between groups ($p=0.0311$; prespecified alpha level of 0.025).
- The comparison of the manipulated AR19 and placebo groups indicated that the abuse potential of manipulated AR19 was higher than that of placebo.

Responder Analysis for the Primary Endpoint

The responder analysis recommended in the 2015 FDA *Abuse-Deterrent Opioids—Evaluation and Labeling* guidance for industry is to test:

$$H_0: p^* \leq 50\% \text{ vs. } H_a: p^* > 50\%$$

at the 2.5% significance level, where p^* denotes the percentage of responders.

The Applicant hypothesized that the majority of subjects (>50%) would be responders, defined as having at least a 10% reduction in maximum Drug Liking for manipulated AR19 compared to amphetamine 40 mg. The Applicant has reported results for the responder analysis using both the completers population, which is a population that did not result in a validated study, and the population that excluded the one outlier subject they identified, which was not done using prespecified criteria. Therefore, the results of those analyses will not be considered further here.

However, the Agency biometrics reviewer found that the number of subjects who were responders (i.e., at least a 10% reduction in maximum Drug Liking for manipulated AR19 relative to amphetamine 40 mg) was not statistically significantly greater than 50% at the appropriate significance level ($p=0.0278$ vs the appropriate significance level of 0.025).

Secondary Analysis

The Applicant did not prespecify key secondary endpoints; however, the biometrics reviewer performed secondary analyses for the modified completer population ($n=33$) for Overall Drug Liking E_{max} , Take Drug Again E_{max} , and High E_{max} , endpoints that are typically evaluated in HAP studies.

[Table 3](#) summarizes the results from the secondary analyses for Overall Drug Liking E_{max} and High E_{max} .

Table 3. Secondary Analysis Results for Overall Drug Liking E_{max} and High E_{max} for the modified Completer Population (n=33)

TRT	Overall Drug Liking		High E _{max}		
	E _{max}	LSMean	StdErr	LSMean	SE
Placebo		54.0	1.9	11.6	6.6
Amphetamine 40 mg		74.7	3.5	60.1	10.9
Manipulated AR19		63.0	4.1	14.5	5.4

Source: Division of Biometrics VI, FDA

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

Table 4 summarizes the results from the secondary analysis for Take Drug Again E_{max}.

Table 4. Secondary Analysis Results on Take Drug Again E_{max} for the modified Completer Population (n=33)

TRT	Mean	SE
Placebo	54.6	2.1
Amphetamine 40 mg	78.8	3.6
Manipulated AR19	64.0	4.9

Source: Division of Biometrics VI, FDA

Abbreviations: TRT, treatment; SE, standard error

The means of Overall Drug Liking E_{max}, Take Drug Again E_{max}, and High E_{max} for amphetamine 40 mg were statistically significantly greater than that of placebo.

Manipulated AR19 had a nominally statistically significant 10% reduction in mean maximum Overall Drug Liking ($p=0.0221$), 20% reduction in mean maximum Take Drug Again ($p=0.0174$), and 45% reduction in mean maximum High ($p=0.0200$) compared to amphetamine 40 mg.

The comparison between manipulated AR19 and placebo was significant for Overall Drug Liking E_{max}, indicating that the overall Drug Liking effect of manipulated AR19 is greater than placebo. However, the comparison of manipulated AR19 and placebo was not significant for Take Drug Again E_{max} or High E_{max}, indicating that the Take Drug Again and High effects of manipulated AR19 are not higher than those of placebo.

Responder Analysis for Secondary Endpoints

The majority of subjects (i.e., more than 50%) did not meet the responder definition (i.e., at least a 10% reduction) for maximum Overall Drug Liking ($p=0.1920$) or Take Drug Again ($p=0.4309$) but did so for maximum High ($p=0.0118$) for manipulated AR19 compared to amphetamine 40 mg.

Abuse-Related Adverse Events

More subjects in the amphetamine API group (8 of 39; 25%) than in the manipulated AR19 (3 of 39; 7.9%) or placebo (0 of 39) groups spontaneously reported AEs of euphoric mood; (i.e., these events were considered adverse, not reinforcing, by the study subjects). Because the HAP study was designed to assess the positive reinforcing effects of intranasal administration of the study treatments on the prespecified endpoints described above, the results of this AE analysis do not alter the overall conclusions.

Overall Conclusions

Regarding the properties of AR19 intended to deter abuse of the formulation by the oral, IN, and IV routes, we conclude the following:

1. Based on the IR properties of the AR19 capsule formulation, AR19 was not intended to, and will not, deter abuse by the oral route, which is the most common route of amphetamine prescription product abuse.
2. Considering that the primary route of abuse of amphetamine-containing products is oral, it is possible that the proposed high strengths of AR19 capsules (30 mg and 40 mg) will be rapidly recognized among people using amphetamine-containing products for recreational purposes. The maximum available strength of the reference standard, Evekeo tablets, is 10 mg; Evekeo is also available as an orally disintegrating tablet, in strengths up to 20 mg.
3. Human abuse potential studies to evaluate the abuse-deterrent effects of manipulated product administered by the IV route cannot be conducted for safety reasons (i.e., due to the effects of IV administration of excipients and other impurities that may arise from manipulation). Therefore, evaluation of the abuse-deterrent effects by the IV route is supported by in vitro syringeability studies. This evaluation requires an understanding of the dose-response curve for IV administration of the active pharmaceutical component, based on human abuse potential data for the API. However, the Applicant did not conduct a pilot study to determine what would constitute a reinforcing IV dose of (\pm)-amphetamine sulfate when injected at a rate commonly used by people who inject drugs. Based on data from the literature, CSS determined that a reasonable minimum reinforcing dose would be 10 mg of amphetamine administered in a small volume over a 60-second period.
4. Syringeability studies showed that, under certain extraction conditions, it was feasible to obtain a solution for injection containing at least approximately 10 mg and 20 mg of amphetamine sulfate per mL when using 20 mg and 40 mg AR19 capsules, respectively. As with the positive control, preparation of a sample suitable for injection using lower-strength capsules was hampered by the lower content of API in these strengths.
5. The assessment of the deterrent effects of a formulation via the IN route of abuse is based on the data collected in HAP studies. The Applicant conducted a HAP study to evaluate the deterrent properties of AR19 when administered IN. The Applicant expected to show a 10% reduction in the reinforcing properties of AR19 IN compared to the positive control (amphetamine sulfate API IN) for primary and secondary endpoints. The Applicant also expected to show that the majority of subjects (>50%) had a $\geq 10\%$ reduction in reinforcing properties of AR19 IN, compared to amphetamine sulfate API IN (responder analysis).

The IN HAP study was not considered to be valid when all completers were analyzed. The Agency conducted a post hoc analysis using criteria that were not prespecified to exclude outlier subjects for exploratory purposes. Using the modified completer population:

- Drug Liking E_{max} (primary endpoint) was not significantly different between AR19 and amphetamine 40 mg
- There was a lack of a consistent pattern of results on the analyses of the secondary endpoints, further weakening the primary endpoint results.
- Taken together, the results of the post hoc analyses in the IN HAP study do not support that the formulation employed for AR19 has significant abuse-deterrent effects, relative to amphetamine sulfate, when administered by the IN route.

8. NONCLINICAL FINDINGS

There are no safety concerns with the proposed drug product formulation when used as intended via the oral route. The safety concerns arise only when the oral product is administered by unintended routes of administration such as intravenous (IV) and intranasal (IN). These concerns are attributed to two excipients: PEO 7M Da and talc.

Previous reports indicate that people who injected abuse deterrent opioid formulations containing HMW PEOs, such as PEO 7M Da, by the IV route experienced adverse events such as anemia, thrombocytopenia, TMA, acute kidney injury, and retinal and cardiac damage ([CDC 2013](#)). Studies conducted in guinea pigs were consistent with these human adverse events ([Hunt et al. 2017](#)). IV and IN (snorting) exposures to talc cause granulomas and pulmonary talcosis (an inflammatory reaction in the lungs that can lead to emphysema) ([Hollinger 1990](#); [Ward et al. 2000](#)). Because of these known risks, the Applicant conducted nonclinical studies and provided published data to evaluate the risks of misuse/abuse of AR19 via the IV and IN routes.

Oral formulations must be manipulated to obtain syringeable material containing the drug substance in order to be injected by the IV route. Such manipulations are evaluated via Category 1 Small Volume Extraction studies. Utilizing various extraction methods (“Conditions”), the Applicant prepared nine different AR 19 extracts to be tested. All nine extracts were tested in an in vitro hemolysis assay; only one extract was tested in vivo.

In an in vitro hemolysis study, the highest degree of hemolysis was observed with an extract from Condition 3, followed by those from Conditions 6 and 4. Although syringeability status of extracts from Conditions 6 and 4 remains unknown, the Applicant noted that the material from Condition 3 was only syringeable when maintained at temperatures that are inappropriate for IV injection into rabbits. The Condition 8 extract was described by the Applicant as the “worst-case” scenario because this condition yielded the maximum amount of syringeable amphetamine. However, under the extraction conditions employed to obtain Condition 8 syringeable material, the majority of the PEO 7M Da was broken down to ≤ 1 M Da, thus lowering its hemolytic potential ([Persich et al. 2020](#)).

Using in vivo studies, Condition 8 AR19 extract and the positive control comparator (uncured PEO 7M Da) were tested in a series of preliminary and pivotal toxicity studies in New Zealand White rabbits. In a preliminary 7-day dose-selection toxicity study, all positive control rabbits survived for the entire span of the study, but histopathological evaluation demonstrated that all of the PEO 7M Da-treated animals had thrombosis at the injection sites, and spleen and kidney findings similar to those previously reported in the literature for guinea pigs that were administered inert ingredient mixture containing primarily HMW PEO ([Hunt et al. 2017](#)). In another preliminary study, the highest dose of AR19 Condition 8 extract (i.e., 84.9 mg/kg of total AR19 extract obtained from three capsules), produced minimal effects on hemolytic parameters and liver enzymes and an increase in liver and spleen weights without microscopic correlates. One of two female rabbits in the study showed marked focal inflammation of the AV node characterized by marked apoptotic cell debris, reactive macrophages, and loss of AV-node myocytes. Although this is a rare finding, the Applicant concluded that this AV node finding was unrelated to AR 19, but rather secondary to the experimental procedures.

Despite the adverse findings observed in the preliminary studies with the positive control and AR19 extract, these findings were not replicated in the 7-day pivotal study. In the pivotal toxicity study, all of the positive control rabbits either died prematurely or were euthanized after a single dose (due to clinical signs such as decreased activity, abnormal gait, and flattened position) within 20 to 30 minutes of dosing. There were no notable adverse findings after AR19 administration up to a dose of 84.9 mg/kg/day.

In view of the failure of the positive control group in the pivotal study, the negative findings with the AR19 extract are considered uninterpretable. In addition, we have multiple review concerns about this study. First, there are not enough published data in the literature to determine whether rabbits were an appropriate animal model for examining toxicities related to IV administration of PEO 7M Da. Second, the extract-mediated toxicities appeared to be different in the preliminary study compared to the pivotal study, though the total amount of PEO administered and exposures were similar. It was evident that the extraction methods yielded different levels of the various molecular weight compounds in the two studies. Third, studies examining the potential toxicity of PEO solutions following IV administration should take into consideration the potential for instability of the PEO in the solutions and confirm what molecular weight was actually administered to the animals. Finally, the toxicity profile for syringeable extracts following other manipulation conditions were not evaluated *in vivo*.

Talc is another excipient in this formulation that has potential toxicity when administered by routes other than oral. In response to the Agency's concerns about the presence of talc, the Applicant determined levels of talc following Category 1 extraction studies. Based on the talc levels, the Applicant calculated safety margins to the toxicities reported in published literature for IV, IN, or intratracheal exposures. The Applicant believes that there is a large safety margin for the adverse findings in animals compared to the levels that will be encountered in humans when the compound is introduced via the IV or the IN route. Overall, they conclude that the levels of talc in the product do not pose a serious concern for IV or IN abuse. Their conclusion is based on what they believe to be small amounts of free talc in the drug product, the amount lost in extraction, their behavioral analysis of people who abuse stimulants (based on their interpretation of the IN HAP study, which they believe shows decreased IN liking of AR19 compared with amphetamine sulfate), and the time and difficulty in preparing AR19 for non-oral abuse.

We note that most of the Applicant's safety margins for talc are not based on the no observed adverse effect level (NOAEL), but rather on the lowest observed adverse effect level (LOAEL) and to a clinical dose of 20 mg, which is not the maximum recommended human dose (MRHD). The proposed MRHD of 40 mg contains 11% more talc than the 20 mg capsule and the discussions here pertain not to labeled drug use, but rather to the misuse of large quantities beyond the MRHD. Although the safety margin is calculated to the estimated amount available for lung deposition due to particle size, the Applicant does not account for the rest of the talc that may be deposited in various portions of the respiratory system. Furthermore, IN administered talc has a biological half-life of 7 to 10 days, which would mean that toxicities that result from such use may be cumulative; therefore, safety margins calculated based on a single use may be overestimated.

Nonclinical Conclusions

From a nonclinical perspective, there are safety concerns about the presence of PEO 7M Da and talc in the AR19 product if this product is to be manipulated and administered via unintended routes of administration. Review of the existing data suggests that there are limitations in the Applicant's risk characterization of AR19, as described here:

- The chemical composition of the syringeable material is not fully known.
- The pivotal IV study in rabbits was inadequate. The lack of survival in the positive control group makes the findings in this study uninterpretable.
- The conducted toxicology studies testing extract from a single condition, Condition 8, do not appear to yield reproducible results.
- The studies are limited in terms of the duration of treatment and number of injections.
- The Applicant's conclusions on the safety of talc are based on the LOAEL (rather than the NOAEL) and the potential exposure from a single, 20-mg dose. This scenario does not consider higher talc exposures from higher AR19 exposures or talc accumulation.

Taking these limitations into consideration and given the knowledge that the conducted nonclinical studies do not fully characterize the risk that may occur when individuals manipulate the product for IV use, we conclude that there is a potential for adverse events to occur should AR19 be manipulated and injected intravenously. We cannot, therefore, eliminate the possibility that adverse effects such as TMA could occur similar to what has been observed with OPANA ER (dose- and duration-dependent toxicity due to PEO accumulation).⁹ Regarding IN use, the talc exposure—and subsequent safety risk—in people who might insufflate AR19 is unclear. The Agency does not agree that talc exposure will always be minimal.

⁹ <https://www.fda.gov/advisory-committees/anesthetic-and-analgesic-drug-products-advisory-committee/briefing-information-march-13-14-2017-joint-meeting-anesthetic-and-analgesic-drug-products-advisory>

9. POSTMARKETING DATA ON STIMULANT USE AND NONMEDICAL USE

The purpose of this section of the FDA's briefing document from the Office of Surveillance and Epidemiology (OSE) is to provide current information on drug utilization and postmarketing data on the prevalence, patterns (including route of administration), correlates (e.g., reasons, sources, polysubstance use), and trends in NMU of prescription stimulants and related morbidity and mortality (in particular Schedule II (CII) stimulants indicated for the treatment of ADHD). This background will provide context for consideration of the potential public health impact of AR19 and other prescription stimulants.

To address this objective, we supplemented our review of information from Applicant-submitted study reports with independent data analyses conducted by OSE. As an orientation to this section:

1. In Section 9.1, we present our key findings by posing some key questions about NMU and related adverse events involving prescription stimulants and responding to these questions based on our review of available postmarket data. Where possible, we also make comparisons to opioid analgesics, as the Applicant has based their development program on the *Abuse-Deterrent Opioids—Evaluation and Labeling* guidance for industry, and opioid analgesics are the only class of drugs containing products labeled as having abuse-deterrent properties.
2. In Section 9.2, we comment on where we agree and disagree with the Applicant's interpretations of the epidemiologic data on stimulant NMU, as described in their NDA submission.
3. In Section 9.3, we discuss some uncertainties about the potential impact of this product and ADF stimulants in general. Many of these questions have arisen from our experience with opioid analgesic ADFs.
4. In Section 9.4, we provide a brief description of data sources and methods, selected results, key data strengths and limitations, and an overall summary of the postmarketing data that supported our responses to the key questions in Section 9.1. A full description of the methods and results are included in Attachment 11.4 for those who would like to review these in more detail.

Note that although OSE reviewed the information contained in the Applicant reports, we did not review or approve protocols for these studies prior to submission of the final reports.

9.1. Key Findings About NMU and Related Adverse Events Involving Prescription Stimulants Based on Recent Postmarket Data

1. Are CII prescription stimulants widely used, and has their use changed over time?
 - CII prescription stimulants are widely used, and the number of CII stimulant prescriptions dispensed from U.S. outpatient retail pharmacies increased from 2008 to 2019, driven by an increase in utilization of mixed amphetamine salt products.
2. How does the utilization of CII prescription stimulants compare to that of prescription opioid analgesics?
 - In 2019, the national estimate of the number of prescription opioid analgesics dispensed from U.S. outpatient retail pharmacies was approximately twice that of prescription stimulants. ADF opioid analgesic prescriptions accounted for only 1 to 2% of all opioid analgesic use.
3. How does the utilization of prescription IR racemic amphetamine sulfate stimulant products compare to that of other prescription stimulant products?
 - IR racemic amphetamine sulfate products accounted for about 0.3% of the overall stimulant market from 2017 through 2019. The most common IR racemic amphetamine sulfate dosage unit strengths were 5 mg (18%) and 10 mg (80%).
4. Is NMU of prescription stimulants a serious public health concern?
 - Although in 2018, approximately 2% of the general U.S. population used prescription stimulants nonmedically in the past year, NMU of prescription stimulants is not as common in the general population as NMU of other prescription classes such as pain relievers and tranquilizers or sedatives.
 - Many of the adverse events reported with nonmedical CII prescription stimulant use were labeled events for the stimulant products or were events associated with drug dependence, and the medical severity of adverse events varied. Cardiovascular effects, cerebrovascular effects, neuropsychiatric and behavioral effects, and pulmonary reactions were some of the most commonly reported adverse events associated with NMU of prescription stimulants across data sources.
 - In 2018, approximately 0.2% of the general U.S. population were estimated to have a stimulant use disorder (not including methamphetamine or cocaine use disorders), with the highest prevalence observed among individuals between the ages of 18 and 25 years. Among individuals admitted to publicly funded treatment programs in 2017, other

amphetamines and other stimulants,¹⁰ not including methamphetamine or cocaine, accounted for fewer than 1% of the primary substances reported.

- Overdose deaths involving psychostimulants, including both illicit and prescription stimulant drugs, are increasing; however, the majority of stimulant overdose deaths from 2010 to 2014 mentioned methamphetamine on the death certificate. In 2016, amphetamines were among the top 15 most commonly involved drugs in drug overdose deaths mentioned on death certificates, but it is unclear what proportion of deaths involving amphetamines specifically involved CII prescription stimulant products.
- In comparison to opioids:
 - The prevalence of CII prescription stimulant NMU in the general U.S. population is roughly half the prevalence of prescription opioid analgesic NMU. However, the proportion of those reporting any use who reported NMU in the past year was greater for prescription stimulants compared to prescription pain relievers, the majority of which are opioid analgesics.
 - In 2016, around 36% of the total ED visits for harms related to NMU of pharmaceuticals involved NMU of prescription opioid analgesics with or without other substances, while around 3% of the total ED visits for harms related to NMU of pharmaceuticals involved NMU of CII prescription stimulants with or without other substances.
 - Among individuals admitted to publicly funded treatment programs for SUD, prescription opioid analgesics as well as opiates other than heroin and nonprescription methadone accounted for over 7% of the primary substances reported, while heroin accounted for over 26% of the primary substances reported. Stimulants other than methamphetamine collectively accounted for <1% of primary substances reported.
 - In 2018, the annual number of overdose deaths involving psychostimulants was lower than the number of overdose deaths that involved opioids. It is important to note that illicit substances such as methamphetamine, cocaine, illicit fentanyl, and heroin were included in the psychostimulant and opioid categories. In 2016, fentanyl, heroin, and cocaine were the top three drugs involved in overdose deaths.

5. Is NMU of prescription stimulants increasing?

- In the United States, the magnitude of NMU of prescription stimulants has remained relatively stable from 2010 through 2018, based on estimates from multiple data sources.

6. Is NMU of prescription stimulants concentrated in a certain age group or subset of the population?

¹⁰ Other amphetamines and other stimulants are not well defined and may include stimulants not prescribed for the treatment of ADHD as well as unknown illicit amphetamines or stimulant drugs.

- NMU of prescription stimulants is concentrated in young adults ages 21 to 25 years and appears to occur more frequently in individuals diagnosed with ADHD.
- There was some evidence from the Applicant that college students and those participating in fraternities and sororities (“Greek life”) may have more NMU of prescription stimulants than non-college students of the same age. However, the causal role of college and Greek life involvement in NMU of prescription stimulants is uncertain.

7. What reasons do people report for NMU of prescription stimulants?

- The primary motivation for most NMU of prescription stimulants is related to improving performance at work or school, staying alert or awake, or helping with concentration, with a minority reporting use to achieve euphoric effects (“to feel good or get high”).
- However, a primary reason “to get high” was reported more frequently by individuals who reported lifetime NMU of prescription stimulants via snorting or injecting routes of administration compared to the oral route of administration.
- When compared to individuals with NMU of prescription pain relievers, a similar proportion of individuals with NMU of prescription stimulants gave their primary reason as “to feel good or get high.”

8. Where do people get their prescription stimulants for NMU?

- Friends/relatives were the most common source of prescription stimulants used nonmedically.
- A greater percentage of individuals reported getting prescription pain relievers for NMU from their own prescription or stolen from a healthcare provider as compared to prescription stimulants.

9. What is the prevalence and public health impact of non-oral (smoking, snorting, injection) use of prescription stimulants?

- The vast majority of individuals who use prescription stimulants nonmedically report using them by the oral route. This is true across all data sources covering general populations, college students, those seeking advice or healthcare, and those being assessed for treatment for SUD.
- A substantial minority of individuals who use prescription stimulants nonmedically report having snorted them. NMU of prescription stimulants via smoking and injection is uncommon. The proportions reporting the different routes of administration vary based on the population and data source. NMU of prescription stimulants via non-oral routes such as snorting, smoking, and injecting was reported more frequently by subgroups such as individuals seeking treatment or being assessed for SUDs and college students who participated in Greek life.

- Between 61% and 89% of individuals who reported NMU of prescription stimulants via non-oral routes started with oral NMU prior to initiating non-oral NMU. Additionally, most respondents that reported non-oral NMU of prescription stimulants also reported oral NMU of prescription stimulants.
- Adverse events varied by routes of administration.
 - NPDS exposure cases with severe related medical outcomes occurred more frequently with injection or nasal/inhalation routes compared to oral routes; however, almost 90% of the total route mentions with more severe medical outcomes were from an oral route of exposure as NMU by oral routes was much more common.
 - Among FAERS cases that reported nonmedical CII prescription stimulant use via non-oral routes, unlabeled adverse events reported with inhalation of CII prescription stimulants included pulmonary toxicity, epistaxis, and pulmonary edema, while those reported with injection of CII prescription stimulants included injection site edema, endocarditis, hepatitis A, and hepatitis C.
- Data from AR19.MA004 suggested that the route patterns reported for NMU of prescription opioid analgesics were similar to those reported for NMU of prescription stimulants, although snorting was more common for NMU of prescription stimulants. However, opioid analgesic products containing hydrocodone or oxycodone in combination with acetaminophen are less commonly snorted than single-entity products yet are the most common opioid analgesics dispensed, hampering comparisons of the overall proportions of NMU via snorting for prescription stimulants and prescription opioid analgesics, as a class.

9.2. Comparison of Applicant and FDA Interpretations of Epidemiologic Data on NMU Patterns

Table 5. FDA Comments on the Applicant's Interpretations of the Epidemiologic Data on NMU of Prescription Stimulants

Applicant Interpretation*	FDA Comments
NMU of prescriptions stimulants, particularly amphetamines, is common and increasing, especially in older adolescents, young adults, and college students.	Partially agree. Data suggest that NMU of prescription stimulants is not as common in the general population as NMU of other prescription drug classes such as pain relievers. Based on most available data sources, the magnitude of NMU of prescription stimulants has remained relatively stable from 2010 through 2018. Among individuals being assessed for or entering treatment, NMU of prescription stimulants may be increasing, but the limitations of these data make interpretation of observed trends difficult. NMU of prescription stimulants is concentrated in young adults ages 21 to 25 years and appears to occur more frequently in individuals diagnosed with ADHD.
Non-oral routes constitute an appreciable amount of NMU.	There was some evidence that college students and those participating in Greek life may have more NMU of prescription stimulants; however, the causal role of college and Greek life involvement in NMU of prescription stimulants is uncertain.
Non-oral NMU of prescription stimulants is associated with more severe medical outcomes and polysubstance use compared to oral NMU.	Partially agree. The vast majority of NMU of prescription stimulants is by the oral route across all data sources. NMU of prescription stimulants via smoking and injection routes of administration is uncommon in the general population. A substantial minority of individuals who use prescription stimulants nonmedically report having snorted them. It is unclear, however, how frequently each route is utilized by individuals who nonmedically use prescription stimulants by multiple routes, because this information is not normally captured. NMU of prescription stimulants via non-oral routes such as snorting, smoking, and injecting were reported more frequently by subgroups such as individuals seeking treatment or being assessed for SUDs, individuals with a history of NMU of prescription stimulants via a non-oral route of administration, and college students who participated in Greek life.
	Agree. More severe medical outcomes occurred more commonly with injection followed by snorting and the oral route of NMU of prescription stimulants. Polysubstance use of other substances, especially illicit drugs, was more common among individuals who reported snorting or injecting prescription stimulants.

Applicant Interpretation*	FDA Comments
Although the predominant motivations for NMU of prescription stimulants are performance enhancement and to get high, the motivation to get high is greater for non-oral NMU of prescription stimulants compared to oral NMU.	The primary motivation for most NMU of prescription stimulants is related to improving performance at work or school, staying alert or awake, or to help with concentration. A greater proportion of individuals who reported NMU of prescription stimulants via snorting or injection reported getting high as their primary motivation.
Individuals with ADHD are at greater risk for NMU and substance use disorder (SUD).	Agree. Limited data suggest that a previous diagnosis of ADHD was associated with higher odds of NMU of prescription stimulants.
Diversion of prescription stimulants is common.	Agree. The most common source of prescription stimulants used nonmedically was from friends or relatives.

Source: FDA-generated table

*These are FDA's understanding of the Applicant's interpretation of these data based on their NDA submission.

Abbreviations: ADF = abuse-deterrent formulation, ADHD = attention deficit hyperactivity disorder, FDA = U.S. Food and Drug Administration, IR = immediate release, NMU = nonmedical use, SUD = substance use disorder

9.3. Key Uncertainties Regarding Public Health Impact, Incorporating Some Observations from the ADF Opioid Analgesic Postmarket Experience

There are several key uncertainties regarding the potential public health risks and benefits of this and other prescription stimulant formulations designed to deter non-oral routes of administration. The Applicant laid out pathways through which their formulation and that of other ADF stimulants may impact public health such as:

- Reducing the supply of prescription stimulants that can be manipulated for non-oral routes of NMU
- Preventing *initiation* of non-oral use and development of SUD in individuals with a history of only oral NMU of prescription stimulants

Whether this formulation could benefit public health via these theoretical pathways is unknown, however. Additionally, this product application includes capsules with dosage strengths of 30 and 40 mg, which are higher than currently marketed racemic amphetamine sulfate products (up to 20 mg). For existing racemic amphetamine sulfate products, the vast majority of prescriptions dispensed are for 5 and 10 mg strengths, with 15 and 20 mg strengths comprising <2%. This product could theoretically drive an increase in NMU if the higher-strength capsules have a higher abuse liability and there is sufficient utilization of those strengths.

Additional questions about ADF stimulants have arisen based on our experience with opioid analgesic ADFs. OxyContin is an oxycodone ER formulation with FDA-approved labeling stating that it was expected to deter NMU via intranasal and injection routes based on premarket studies, and it is the only prescription product with abuse-deterrent labeling that has been

formally evaluated in postmarketing requirement (PMR) studies, to date. At a recent Advisory Committee meeting ([September 10 and 11, 2020](#)), FDA discussed the results of PMR studies and relevant findings from the published literature to evaluate whether OxyContin's reformulation actually deterred abuse by the expected routes in the postmarketing setting and whether the reformulation resulted in an overall public health benefit.

Some questions that have arisen for opioid analgesic ADFs that may be relevant to ADF stimulants are:

1. Will the abuse-deterrent properties actually deter abuse of that specific product via the targeted routes in real-world (postmarketing) settings?
2. Will the abuse-deterrent properties result in meaningful reductions in NMU-related harms, such as addiction, overdose, or injection-related harms such as HIV or hepatitis C transmission?
3. Could there be unintended consequences of the abuse-deterrent formulation such as:
 - Excipient harms related to snorting or injection of the ADF product
 - Substitution with other potentially more dangerous substances (particularly illicit stimulants)
 - Shifts to a more dangerous route of administration, for example if snorting is deterred more effectively than injection

The Applicant proposed a postmarketing study plan to monitor for adverse events related to their product (NMU, overdose, diversion, and adverse consequences of injection due to PEO) in routine pharmacovigilance data, several publicly available federal data sources, PCCs, and by monitoring of Internet sites, local news media, and the medical literature. However, we have learned from the experience with ADF opioid analgesics that there are many challenges to answering the questions outlined above via postmarketing data. For example:

- Many data sources cannot differentiate ADF products from other products with the same API.
- Concurrent interventions and evolving patterns of NMU of substances can confound studies of trends over time.
- There are many challenges with data and methodology, and postmarketing studies likely support only qualitative, rather than quantitative, inferences regarding abuse deterrence.
- There is potentially a long time lag from introduction of a new ADF product to the market to a time when it may be feasible to assess the effectiveness of its abuse-deterrent properties, particularly in products with low market uptake. Utilization of the product

may never be sufficient to conduct robust studies of the effectiveness or understand the broader public health impact of the ADF.

9.4. Data Sources and Methods, Selected Results, Key Data Strengths and Limitations, and Summary of Postmarketing Data

9.4.1. Data Sources and Methods

1. Drug Utilization

We used nationally-estimated sales distribution, dispensed prescriptions, and office-based physician survey data from the following proprietary databases available to the Agency to conduct analyses of the drug utilization patterns for CII prescription stimulants over the most recent 12-year period (2008 to 2019). Time periods assessed varied based on data availability. We also analyzed drug utilization patterns for prescription opioid analgesics, where possible, to provide context.

- IQVIA, National Sales Perspective
- IQVIA, National Prescription Audit
- IQVIA, Total Patient Tracker
- Syneos Treatment Answers

2. Pharmacovigilance: Spontaneous reports via the FDA Adverse Event Reporting System (FAERS)

We searched the FAERS database from January 1, 2007, through April 23, 2020, to identify postmarketing case reports of nonmedical CII prescription stimulant use via a non-oral route. We also searched the medical literature to identify any case reports of nonmedical CII prescription use and summarized the published findings on the morbidity related to NMU of CII prescription stimulants.

3. Epidemiologic Review of NMU

We examined multiple epidemiologic data sources available to FDA to describe patterns of NMU and related adverse outcomes associated with CII prescription stimulants, as well as illicit stimulants when possible ([Table 6](#)). We also included results of analyses from Applicant-submitted reports that helped to address the key questions related to this section of FDA's briefing document. Applicant-submitted reports came from studies conducted by various academic researchers, internet panel survey companies, and data vendors. We refer to those studies by the report numbers AR19.MAXXX, where XXX is the report number. We did not include results of analyses from the Applicant-submitted reports where we had conducted a more recent or rigorous analysis of the same data source, where we had scientific concerns about the methodology used, or where the results did not address the key questions related to this section of FDA's briefing document. We also provided patterns of prescription opioid analgesic NMU, where possible, for context, given that there are several

marketed opioid analgesics with approved product labeling stating that they have properties expected to deter abuse via certain routes of administration. Data included in this section span from 1980 through 2019; however, for most data sources we focused on the most recent years of available data.

In OSE's review of the epidemiologic data, we generally used the term *nonmedical use (NMU)*, which combines the concepts of misuse and abuse. We provide the original definitions from each data source that we considered under the term *NMU* in [Table 6](#).

Table 6. Overview of Epidemiologic Data Sources and Studies on NMU of Prescription Stimulants and Other Drugs That Were Conducted by FDA or from Applicant Reports

FDA Data			
Data Source	Source/Population	Use of Data	Definition of NMU
NSDUH, 2015–2018	Nationally representative household survey General U.S. population, persons aged 12 years or older	<ul style="list-style-type: none"> • Scale of NMU • Polysubstance use • Reasons for NMU • Source for NMU • Trajectory for NMU 	Misuse: Use in any way not directed by a doctor, including use without a prescription of one's own; use in greater amounts, more often, or longer than told to take a drug; or use in any other way not directed by a doctor.
MTF, 2013–2019	School-based survey General U.S. population; persons in 8 th , 10 th , 12 th grades	<ul style="list-style-type: none"> • Scale of NMU 	Use: On your own—that is, without a doctor telling you to take them.
AAPCC, NPDS, 2001–2018	NPDS cases from calls to U.S. Poison Control Centers People seeking advice regarding drug exposures	<ul style="list-style-type: none"> • Scale of NMU • Routes of administration • Polysubstance use • Morbidity of NMU 	NMU: Includes: Intentional – Misuse: “An exposure resulting from the intentional improper or incorrect use of a substance for reasons other than the pursuit of a psychotropic effect.” Intentional – Abuse: “An exposure resulting from the intentional improper or incorrect use of a substance where the victim was likely attempting to gain a high, euphoric effect, or some other psychotropic effect.” This includes recreational use of a substance for any effect.
NEISS-CADES, 2016–2018	Nationally representative sample of emergency department visits for adverse effects of pharmaceutical products	<ul style="list-style-type: none"> • Scale of NMU • Polysubstance use • Morbidity of NMU 	NMU: Includes: <ul style="list-style-type: none"> • Documented abuse: Clinician diagnosis of abuse or documented recreational use. • Therapeutic misuse: Documented therapeutic intent, but the pharmaceutical was not used as directed. • Overdoses without documentation of therapeutic intent, self-harm, abuse, or misuse.

NEISS-CADES – Published Analysis by Geller et al., 2019*, January 2016–December 2016	Nationally representative sample of ED visits for adverse effects of pharmaceutical products	• Morbidity of NMU	NMU: Includes: <ul style="list-style-type: none">• Documented abuse: Clinician diagnosis of abuse or documented recreational use.• Therapeutic misuse: Documented therapeutic intent, but the pharmaceutical was not used as directed.• Overdoses without documentation of therapeutic intent, self-harm, abuse, or misuse.
TEDS, 2007–2017	Nonrepresentative, dynamic population sample of individuals admitted for abuse of alcohol and/or drugs in facilities that report to state administrative data systems, aged 12 years and older	• Scale of NMU	Primary Substance: The substance that led to the treatment admissions for substance use.
NAVIPPRO®, ASI-MV®, 2013–2019	Nonrepresentative, dynamic population sample of individuals being assessed or seeking treatment for SUD, aged 17 years and older	• Scale of NMU** • Routes of administration**	Abuse/NMU: Use of the specified prescription product in a way not prescribed by your doctor, via alternative routes of administration, and/or obtained from sources not associated with a prescriber.
NVSS-MCD, 1999–2018	Coded data on drug classes involved in U.S. overdose deaths	• Mortality of NMU	Overdose deaths: Identified using codes from the International Classification of Diseases, Tenth Revision. <ul style="list-style-type: none">• Psychostimulants with abuse potential (T43.6)• Heroin (T40.1)• Natural and semisynthetic opioids (T40.2)• Methadone (T40.3)• Synthetic opioids excluding methadone (T40.4)
DIM, 2010–2014	Drugs mentioned in literal text of U.S. death certificates as contributing to the death	• Mortality of NMU	Drugs of interest <ul style="list-style-type: none">• Amphetamine• Dexmethylphenidate• Dextroamphetamine• Lisdexamfetamine• Methamphetamine• Methylphenidate
<i>Applicant-Submitted Data</i>			
Data Source	Source/Population	Use of Data	Definition of NMU
AR19.MA003 – A Report of Adult ASI-MV® Data, 2010–2017	Nonrepresentative, dynamic population sample of individuals being assessed or seeking treatment for	• Scale of NMU • Routes of administration • Source for NMU	NMU: Determined by an algorithm from responses given during a computer-administered interview. The questions asked were whether the medication was obtained from their own

	SUD, aged 18 years or older		prescription; the medication had been used via an alternate route of administration (i.e., not as prescribed); used in a way not prescribed by the doctor, but for the way it makes one feel and not for the treatment of the drug's indicated disease.
AR19.MA003 – A Report of Adolescent CHAT® Data, 2010–2017	Nonrepresentative, dynamic population sample of adolescents seeking treatment for substance abuse, aged 18 years or younger	<ul style="list-style-type: none"> • Scale of NMU • Routes of administration • Source for NMU 	NMU: Use not as prescribed or to get high.
AR19.MA004, An Online Survey of the General U.S. Population Conducted by the Internet Panel Company YouGov, July–September 2018	<p>Anonymous internet survey</p> <p>General U.S. population, persons aged 18 to 49 years</p>	<ul style="list-style-type: none"> • Scale of NMU • ADHD and NMU • Routes of administration • Polysubstance use • Reasons for NMU • Risk factors for NMU • Source for NMU • Trajectory for NMU 	NMU: Use for any reason, even once, without your own prescription; Use in ways other than prescribed (such as taking more than prescribed, more often than prescribed, or for any other reason/way than prescribed); Use for the feeling or experience the medication caused (such as feeling of being high, enhancement of other drugs, prevention or treatment of withdrawal symptoms or other feelings).
AR19.MA008, An Online Survey of Adult Reddit Users with a History of Nonoral Prescription Stimulant Use, February–September 2019	<p>Anonymous internet survey</p> <p>Persons aged 18 years or older with a history of NMU of prescription stimulants, via at least one nonoral route of administration</p>	<ul style="list-style-type: none"> • Scale of NMU • Routes of administration • Polysubstance use • Trajectory for NMU 	<i>See AR19.MA004 definition.</i>
AR19.MA010, An Anonymous In-Person Interviewer-Facilitated Survey of General Population Youth, Conducted by the Substance Abuse Training Center in Public Health at the University of Florida, August–November 2018	<p>Anonymous in-person youth survey</p> <p>General population youth; persons aged 10 to 17 years at public venues (e.g., malls, arcades) from six cities in three U.S. states</p>	<ul style="list-style-type: none"> • Routes of administration • Reasons for NMU • Source for NMU 	NMU (main definition): Taking the stimulant product nonorally, taking the stimulant product from someone else, or taking the stimulant product more than prescribed in the past 30 days or in your lifetime but not in the past 30 days.
AR19.MA011 – A Report of NSDUH Data Conducted by Pinney Associates, 2010–2018	<p>Nationally representative household survey</p> <p>General U.S. population, persons aged 12 years or older</p>	<ul style="list-style-type: none"> • Scale of NMU 	Misuse: Use in any way not directed by a doctor, including use without a prescription of one's own; use in greater amounts, more often, or longer than told to take a drug; or use in any other way not directed by a doctor.

AR19.MA011 – A Report of MTF Data Conducted by Pinney Associates, 1980–2018	School-based survey General U.S. population; persons in 8 th , 10 th , 12 th grades	• College enrollment and NMU	Use: On your own—that is, without a doctor telling you to take them.
AR19.MA012, An Online Survey of the General U.S. College-Aged Population Conducted by the Internet Panel Company YouGov, July–September 2018 and February–September 2019	Anonymous internet survey General U.S. population, persons aged 18 to 26 years	• Scale of NMU • College enrollment and NMU • Routes of administration • Polysubstance use • Reasons for NMU • Source for NMU	<i>See AR19.MA004 definition.</i>
NOMAD, An Online Survey of Adults with a History of Non-oral Prescription Stimulant Use Conducted by the research Organization W2O/Marketech, August–September 2018	Anonymous internet survey Persons aged 18 years or older that had used an ADHD prescription stimulant, via a non-oral route of administration	• ADHD and NMU • Routes of administration • Trajectory for NMU	Abuse: taken any prescription ADHD stimulant, even once, for any reason other than treating ADHD symptoms, such as staying awake, getting high, increasing energy, enhancing performance, etc.

Note: ** This includes results a published analysis of 2016 NEISS-CADES data (Geller et al. 2019)

Note: *** indicates that the analysis only included prescription opioid analgesics.

Abbreviations: ADHD = attention deficit hyperactivity disorder, SUD = substance use disorder, U.S. = United States, AAPCC = American Association of Poison Control Centers, ASI-MV® = Addiction Severity Index-Multimedia Version, CHAT® = Comprehensive Health Assessment for Teens, DIM = National Data on Drug-Involved Mortality, FDA = U.S. Food and Drug Administration, MTF = Monitoring the Future, NAVIPPRO® = National Addictions Vigilance Intervention and Prevention Program, NEISS-CADES = National Electronic Injury Surveillance System—Cooperative Adverse Drug Event Surveillance, NMU = nonmedical use, NPDS = National Poison Data System, NSDUH = National Survey on Drug Use and Health, NVSS-MCD = National Vital Statistics System-Multiple Cause of Death Database, TEDS = Treatment Episode Data Set

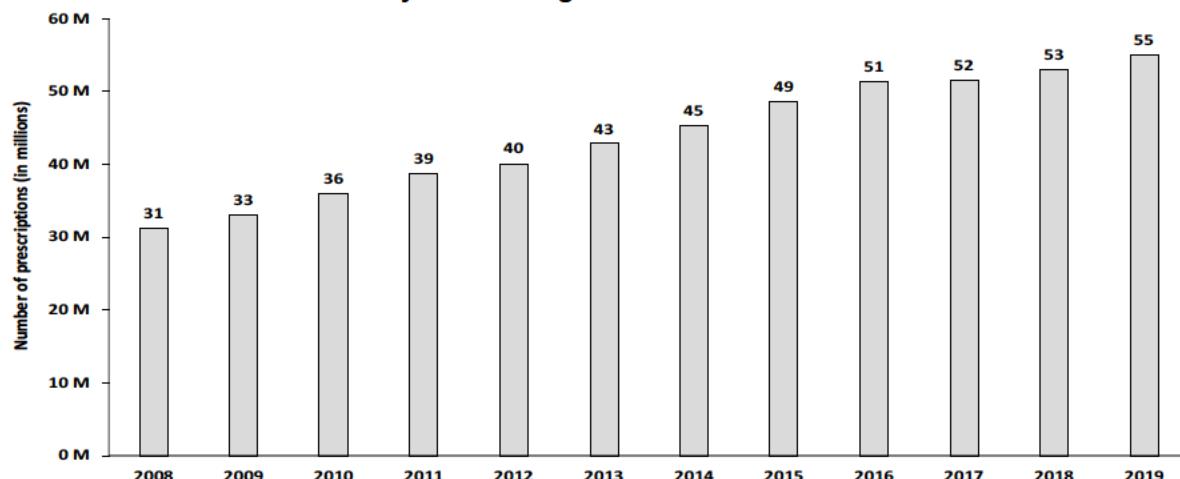
Applicant Report Titles: AR19.MA003 = Analysis of Prescription Stimulants in ASI-MV® and CHAT®, AR19.MA004 = Analysis of Survey of Nonmedical Use of Prescription Medications among the General Population, AR19.MA008 = Understanding Patterns of Prescription Medication Abuse and Progression to Nonoral Routes of Administration, AR19.MA010= The Study of Non-oral Administration of Prescription Stimulants (SNAPS), AR19.MA011 = Public Health Rationale for AR-19 (Amphetamine Sulfate Immediate Release Abuse Deterrent) Capsules, AR19.MA012 = Nonmedical Use of Prescription Medications in College Students Involved in Greek Life (Fraternity or Sorority), NOMAD = The NOMAD Nonoral Abuse Survey: Elucidation of Pathways to Nonoral ADHD Prescription Stimulant Abuse

9.4.2. Results

9.4.2.1. Drug Utilization of CII Stimulants

Overall, CII stimulant prescriptions dispensed from U.S. outpatient retail pharmacies increased by 76%, from an estimated 31 million prescriptions in 2008 to 55 million in 2019 (Figure 2).

Figure 2. National Estimates of Prescriptions Dispensed for CII Stimulants From U.S. Outpatient Retail Pharmacies From January 2008 through December 2019

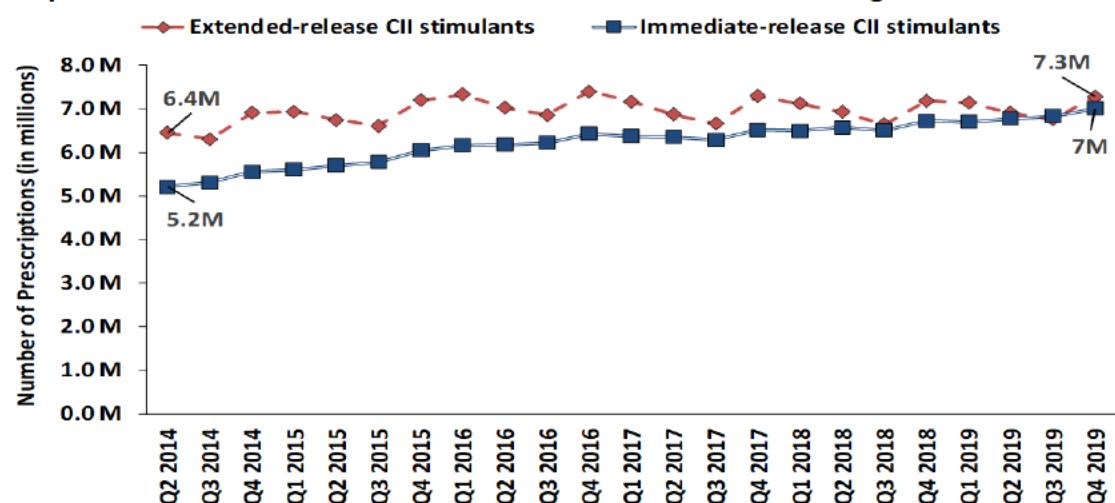


Source: FDA analysis of National Prescription Audit Patient Insights™. 2008–2019. Extracted April 2020. File: 2020-95 NPA stimulants by age Apr-2020.xlsx Source: IQVIA, National Prescription Audit™. 2008–2019. Extracted April 2020. File: 2020-95 NPA stimulants by age Apr-2020.xlsx

Abbreviations: CII = Schedule II, U.S. = United States

Analyses of recent time periods, from the second quarter of 2014 to the fourth quarter of 2019, were conducted to assess more granular data. From the second quarter of 2014 to the fourth quarter of 2019, prescriptions dispensed for IR CII stimulants and extended-release (ER) CII stimulants increased by 34% and 14%, respectively ([Figure 3](#)).

Figure 3. National Estimates of Prescriptions Dispensed for IR and ER CII Stimulants from U.S. Outpatient Retail Pharmacies from the Second Quarter of 2014 through the Fourth Quarter of 2019



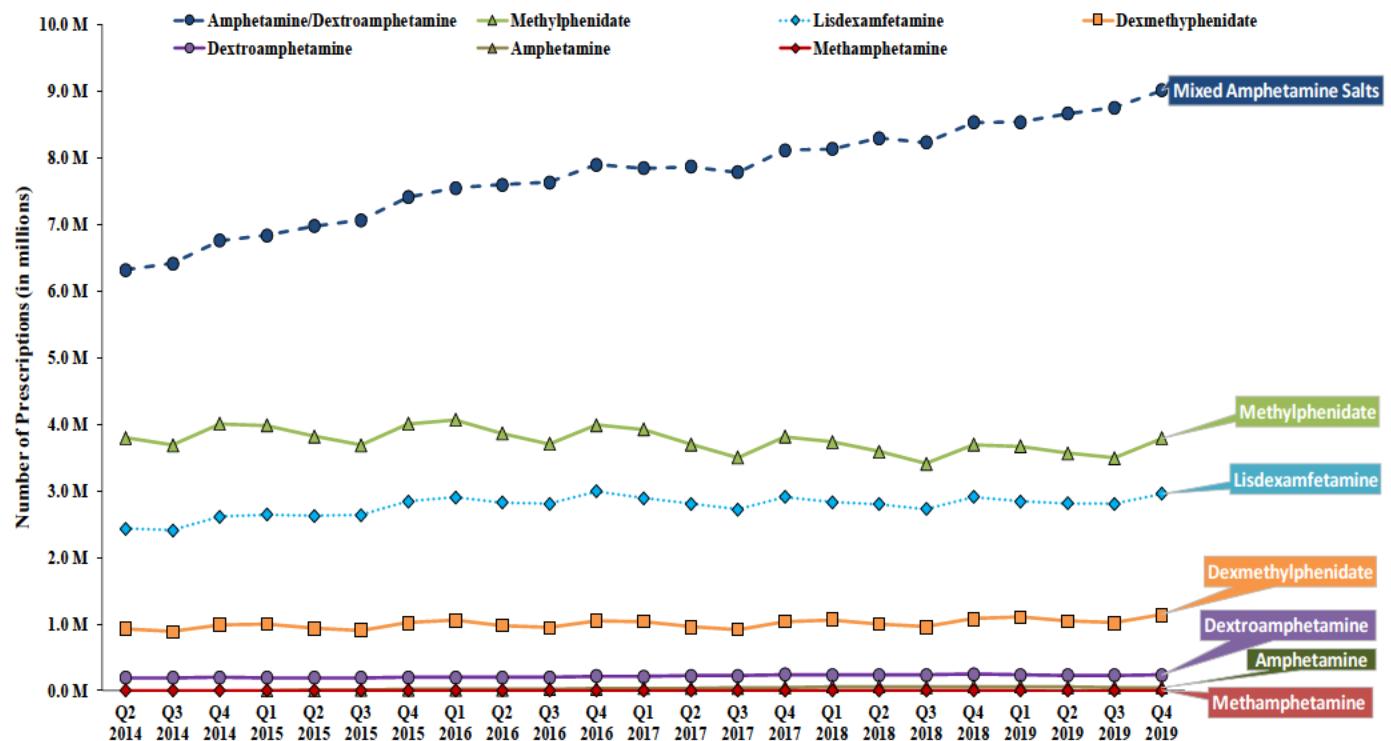
Source: FDA analysis of IQVIA, National Prescription Audit™. 2014–2019. Extracted March 2020. File: 2020-95 NPA stimulants TRx IR vs. ER NPA Mar-11-2020.xlsx

Abbreviations: CII = Schedule II, ER = extended release, IR = immediate release, U.S. = United States

An increase in mixed amphetamine salt products (43%), which include a mixture of salts containing amphetamine and dextroamphetamine, largely drove the overall increase from 2014 through 2019, with approximately 9 million prescriptions dispensed in the fourth quarter of 2019 ([Figure 4](#)). Racemic amphetamine sulfate (“amphetamine”) accounted for a small share of the

overall stimulant market (53,000 prescriptions) in the fourth quarter of 2019 and has remained relatively steady throughout the observation period. The vast majority of IR racemic amphetamine sulfate prescriptions dispensed in 2019 were for 5- and 10-mg-strength tablets.

Figure 4. National Estimates of Prescriptions Dispensed for CII Stimulants, Stratified by Drug, from U.S. Outpatient Retail Pharmacies from the Second Quarter of 2014 to the Fourth Quarter of 2019

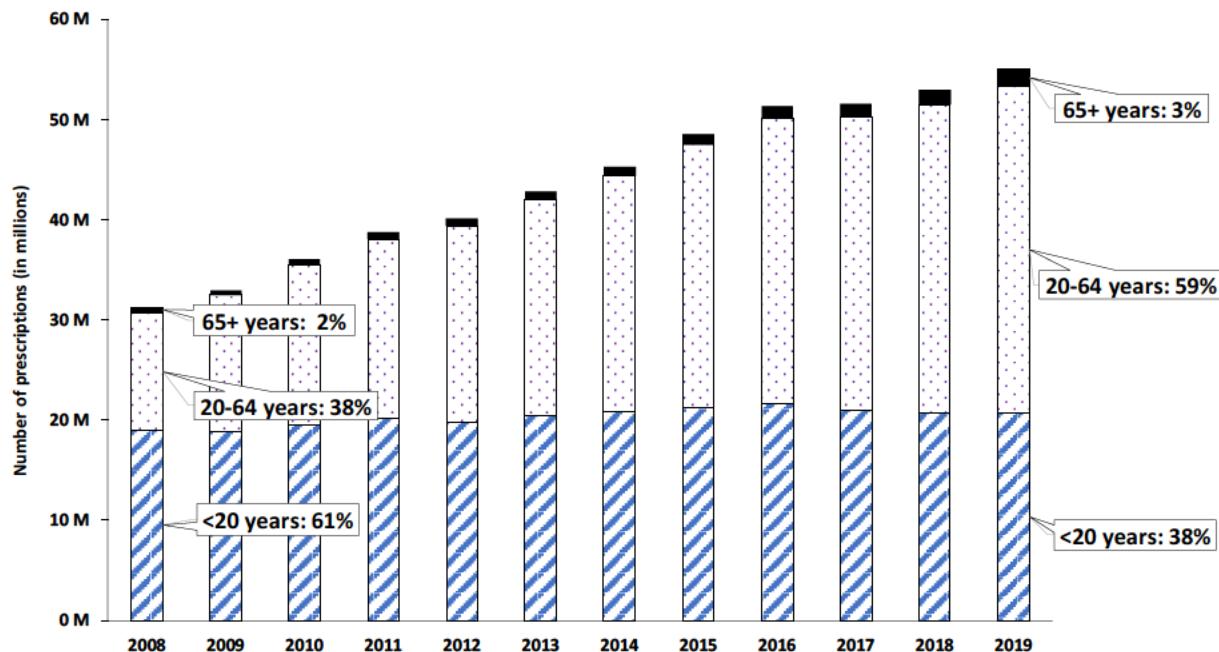


Source: FDA analysis of IQVIA, National Prescription Audit™. 2014–2019. Extracted March 2020. File: 2020-95 NPA stimulants TRx molecule_1_Mar-09-2020.xlsx

Abbreviations: CII = Schedule II, U.S. = United States

Figure 5 displays the national estimates of prescriptions dispensed for CII stimulants, stratified by patient age (<20 years, 20 to 64 years, and ≥65 years), from 2008 through 2019, yearly. The largest increase in prescriptions dispensed proportionally and in the number of prescriptions was observed for patients aged 20 to 64 years, from accounting for 38% (11.8 million prescriptions) of total prescriptions in 2008 to 59% (32.7 million prescriptions) in 2019.

Figure 5. National Estimates of Prescriptions Dispensed for CII Stimulants, Stratified by Patient Age (<20 Years, 20 to 64 Years, and ≥65 Years), from U.S. Outpatient Retail Pharmacies, January 2008 through December 2019

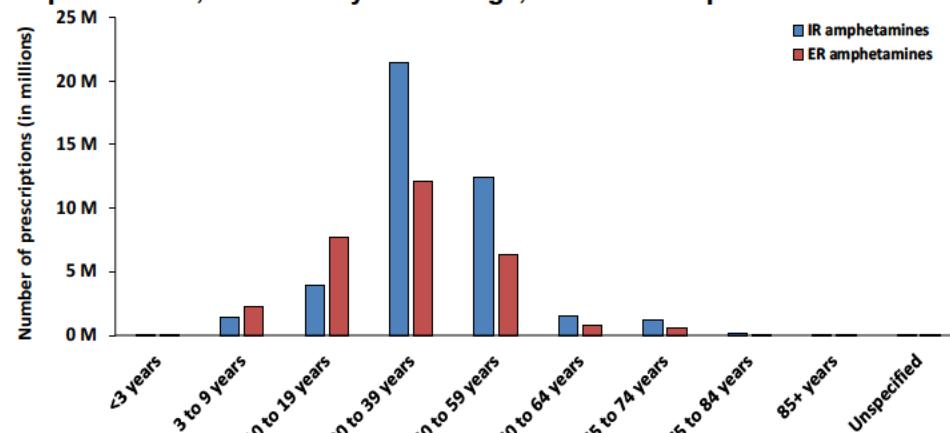


Source: FDA analysis of IQVIA, National Prescription Audit Patient Insights™. 2008-2019. Extracted April 2020. File: 2020-95 NPA stimulants by age Apr-2020.xlsx Source: IQVIA, National Prescription Audit™. 2008-2019. Extracted April 2020. File: 2020-95 NPA stimulants by age Apr-2020.xlsx

Abbreviations: CII = Schedule II, U.S. = United States

CII prescription stimulant products were most frequently dispensed to patients 20 to 39 years old, followed by patients 6 to 12 years old and patients 13 to 19 years old. [Figure 6](#) shows that from January 2018 to December 2019, IR amphetamine prescriptions were frequently dispensed to patients 20 to 74 years old while ER amphetamine prescriptions were more frequently dispensed to pediatric patients 3 to 19 years old. Patients 20 to 39 years old were dispensed almost twice as many prescriptions for IR formulations as for ER formulations.

Figure 6. National Estimates of Prescriptions Dispensed for IR Amphetamines or ER Amphetamines, Stratified by Patient Age, from U.S. Outpatient Retail Pharmacies, 2018 to 2019

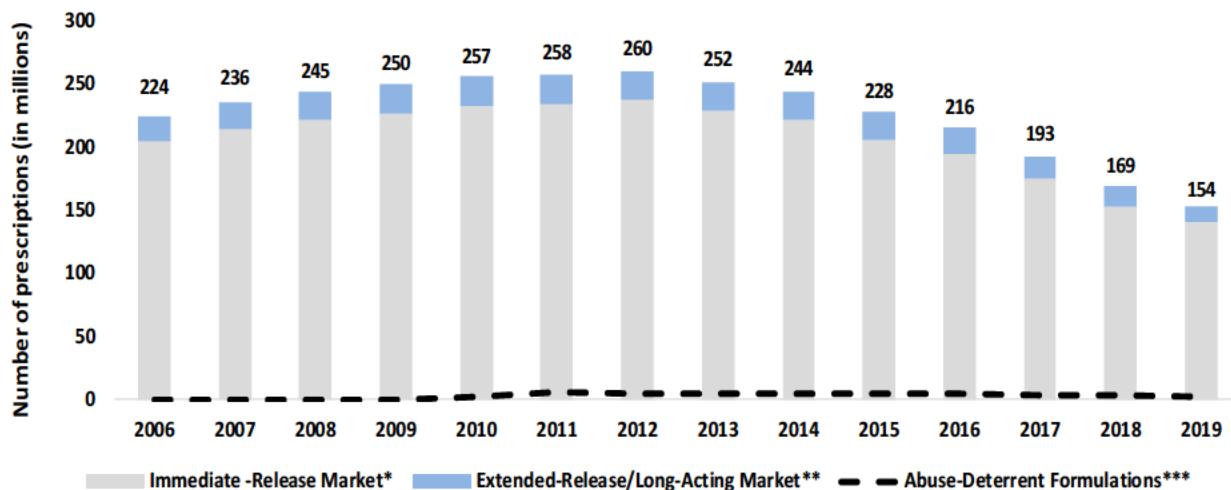


Source: FDA analysis of IQVIA, National Prescription Audit™. 2018-2019. Extracted July 2020. File: 2020-95 NPA amphetamine IR vs ER by age Jul-09.xlsx

Abbreviations: ER = extended release, IR = immediate release, U.S. = United States

As shown above, prescriptions for CII stimulants dispensed were for both IR and ER formulations, while prescriptions for opioid analgesics were predominantly dispensed for IR formulations ([Figure 7](#)). ADF opioid analgesic products have represented a very small proportion of the total opioid analgesic market since 2009, accounting for approximately 1 to 2% of total opioid analgesic prescriptions dispensed through U.S. outpatient retail pharmacies, annually.

Figure 7. Nationally Estimated Number of Prescriptions Dispensed for Opioid Analgesic Products[†], Stratified by Formulation, from U.S. Outpatient Retail Pharmacies, 2006 to 2019



Note: ** indicates IR formulations that include oral solids, oral liquids, rectal, nasal, and transmucosal formulations.

Note: *** indicates ER/long-acting formulations that include oral solids and transdermal patches.

Note: **** indicates abuse-deterrent formulation opioid products, which include Arymo ER, Embeda ER, Hysingla ER, Morphabond ER, Xtampza ER, OxyContin ER Reformulated (Approval in April 2010), RoxyBond IR.

Note: † includes all CSA opioid analgesics.

Note: These data include noninjectable opioid analgesics only. Opioid-containing cough-cold products and opioid-containing medication-assisted treatment products are not included.

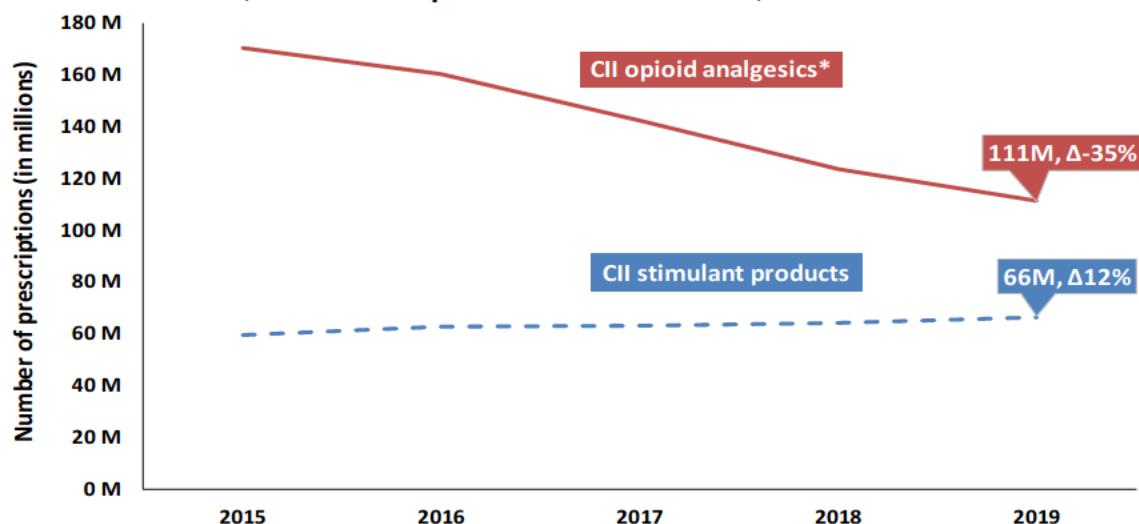
Source: FDA analysis of IQVIA, National Prescription Audit (NPA) and static data 2006-2011. January 2006-December 2019. Static data extracted March 2017, 2012-2017 data extracted February 2018, 2018 data extracted March 2019, 2019 data extracted January 24, 2020.

File: 2020-95 NPA Opioid Slide Deck ALL for ADFs Total IR and ER TRx Update for 2019 1-24-2020 (003).xlsx

Abbreviations: ER = extended release, IR = intermediate release, U.S. = United States

The difference in the number of prescriptions for CII opioid analgesics and stimulant products has narrowed in recent years ([Figure 8](#)). Since 2015, estimated opioid analgesic prescriptions have decreased 35% to 111 million while CII stimulant product prescriptions have increased 12% to 66 million in 2019.

Figure 8. National Estimates of Prescriptions Dispensed for CII Opioid Analgesics and CII Stimulant Products, from U.S. Outpatient Retail Pharmacies, 2015 to 2019



Source: FDA analysis of IQVIA, National Prescription Audit™. 2019. Extracted July 2020. File: 2020-95 NPA stimulants vs. opioids.xlsx

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

Abbreviations: CII = Schedule II, U.S. = United States

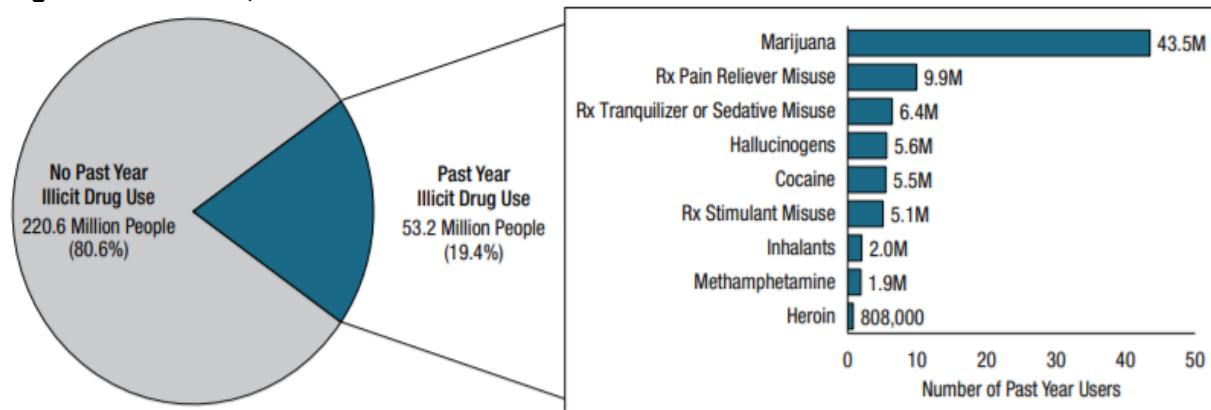
9.4.2.2. Postmarketing Data on NMU and Related Outcomes Involving CII Stimulants

9.4.2.2.1. Scale of NMU of Prescription Stimulants

Prevalence of Prescription Stimulant NMU in the General Population

Data from the most recent available year (2018) of the National Survey on Drug Use and Health (NSDUH) estimated that 5.1 million people aged 12 years or older, or approximately 2% of the population, nonmedically used CII prescription stimulants in the past year ([Figure 9](#)). Similarly, approximately 3% of respondents of the Applicant-submitted general population survey, AR19.MA004, reported NMU of prescription stimulants in the past year. Amphetamine products, followed by methylphenidate products, were the most commonly reported stimulant active pharmaceutical ingredient (APIs) by NSDUH respondents who reported past-year use and NMU of prescription stimulants. This pattern was also seen among AR19.MA004 survey respondents who reported any lifetime use of prescription stimulants. Although data collected from NSDUH suggested that NMU of prescription stimulants is not as common in the general population as is NMU of pain relievers (i.e., opioid analgesics), the proportion of NMU in the past year among those with any use was greater for prescription stimulants (28.4%) as compared to prescription pain relievers (11.5%).

Figure 9. Past-Year Illicit Drug Use among People Aged 12 Years or Older, National Survey on Drug Use and Health, 2018



Source: Center for Behavioral Health Statistics and Quality. Results from the National Survey on Drug Use and Health, 2018. Retrieved from <https://www.samhsa.gov/data/>.

Note: The estimated numbers of past year users of different illicit drugs are not mutually exclusive because people could have used more than one type of illicit drug in the past year.

Note: Illicit drug use included use of marijuana, cocaine (including crack), heroin, hallucinogens, inhalants, methamphetamine, or misuse of prescription (e.g., pain relievers, tranquilizers, stimulants, and sedatives).

Note: Misuse of prescription drugs is defined as use in any way not directed by a doctor, including use without a prescription of one's own; use in greater amounts, more often, or longer than told; or use in any other way not directed by a doctor.

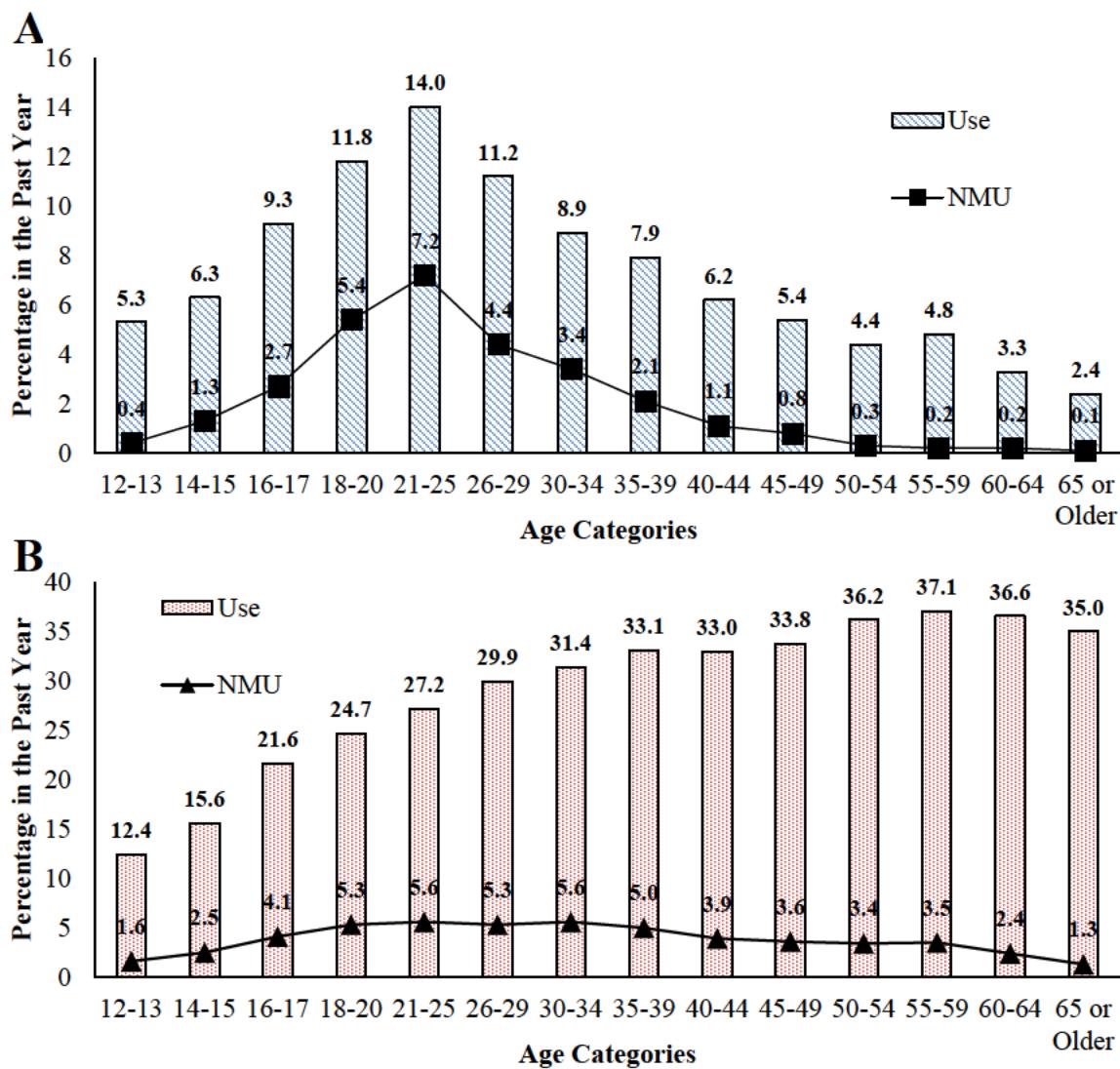
Abbreviation: Rx = prescription

Despite a relatively consistent level of prescription stimulant NMU observed between 2015 and 2018 among adults aged 12 years or older in NSDUH, the estimated number of individuals initiating prescription stimulant NMU in the past year across the same time period dropped from approximately 1.3 to 0.9 million individuals.

Prevalence of Prescription Stimulant NMU in Young Adults and Adolescents

NMU of prescription stimulants is most common in adolescents and young adults. According to 2018 NSDUH data, use and NMU of prescription stimulants was highest among people aged 21 to 25 years and steadily decreased with increasing age ([Figure 10A](#)). However, unlike prescription stimulants, a smaller peak in prescription pain reliever NMU was observed among people aged 21 to 25 years with only small decreases in NMU with increasing age ([Figure 10B](#)). Similar patterns of prescription stimulant NMU across age groups were also seen among National Poison Data System (NPDS) exposure cases from calls to Poison Control Centers (PCCs) for NMU of prescription stimulant exposures and among emergency department (ED) visits due to adverse events involving NMU of prescription stimulants.

Figure 10. Past-Year Use and NMU of (A) Prescription Stimulants and (B) Prescription Pain Relievers among People Aged 12 Years and Older, by Age Categories, National Survey on Drug Use and Health, 2018



Source: FDA-generated figure. Center for Behavioral Health Statistics and Quality. Results from the National Survey on Drug Use and Health, 2018. Retrieved from <https://www.samhsa.gov/data/>.

Note: Use of prescription drugs is defined as the use of one's own prescription medication as directed by a doctor or NMU of prescription drugs. Note: NMU of prescription drugs is defined as use in any way not directed by a doctor, including use without a prescription of one's own; use in greater amounts, more often, or longer than told; or use in any other way not directed by a doctor. Abbreviation: NMU = nonmedical use

Data collected in NSDUH between 2015 and 2018 also show that the percentage of past-year prescription stimulant NMU has decreased by over 20% in individuals aged 12 to 17 years while remaining relatively steady for individuals between the ages of 18 and 25 years and those older than 26 years. Similar reductions in the prevalence of prescription stimulant NMU were observed among adolescents enrolled in eighth, tenth, and twelfth grades who responded to Monitoring the Future (MTF) surveys between 2013 and 2019.

Prevalence of Prescription Stimulant NMU in College Students

Among adolescents and young adults, prescription stimulant NMU varied by college enrollment status. AR19.MA012 survey data showed that past-year NMU of prescription stimulants was greater in individuals enrolled in college (4.4%) compared to those that were not enrolled in college (1.9%). In addition, among individuals enrolled in college, those participating in Greek life¹¹ were 3.6 times as likely to report past-year prescription stimulant NMU as college students that did not participate in Greek life.

Prevalence of Prescription Stimulant NMU in People with ADHD

Psychiatric comorbidities, including ADHD, were more common among individuals reporting prescription stimulant NMU than among individuals with NMU of prescription drugs other than stimulants or among individuals with no NMU of any prescription drug. For example, among AR19.MA004 survey respondents aged 18 to 49 years, a higher percentage of individuals with NMU of prescription stimulants reported diagnoses of depression (64%), anxiety (62%), and ADHD (38%) compared to individuals with NMU of prescription drugs other than stimulants (48%, 49%, and 10%, respectively) and individuals without NMU of prescription drugs (29%, 29%, and 8%, respectively).

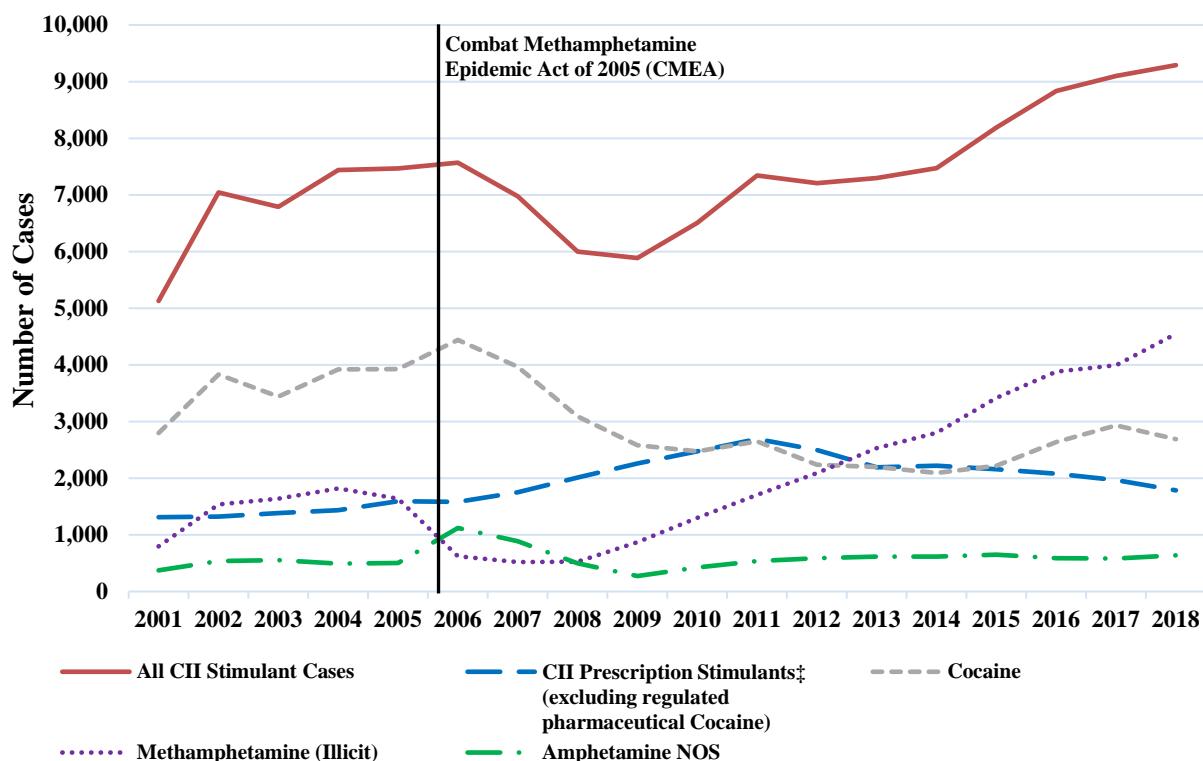
The prevalence of NMU differed between individuals with and without a diagnosis of ADHD for prescription stimulants and other prescription drugs. Among AR19.MA004 respondents diagnosed with ADHD, 8.7% reported NMU of prescription stimulants in the past 30 days and 8.8% reported NMU of prescription opioid analgesics in the past 30 days, while only 1.0% and 3.0% of respondents without a diagnosis of ADHD reported NMU in the past 30 days of prescription stimulants and prescription opioid analgesics, respectively. However, the percentage of respondents enrolled in the NOMAD survey who reported oral NMU of a prescription stimulant prior to their first nonoral NMU of prescription stimulants were similar regardless of ADHD diagnosis.

Trends in NMU of Prescription Stimulants Among People Seeking Advice or Healthcare

Overall, NPDS exposure cases involving NMU of prescription or illicit stimulants increased from 2001 to 2018, largely driven by steady increases in cases involving illicit methamphetamine, beginning around 2008 ([Figure 11](#)). Prescription stimulant NMU cases peaked in 2011 and slowly decreased through the end of 2018.

¹¹ ‘Greek life’ refers to respondents enrolled in college who also participate in fraternities and sororities.

Figure 11. National Poison Data System Exposure Cases Involving NMU of Prescription and Illicit Stimulants, 2001 to 2018



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

Note: '‡' indicates CII stimulants only. Prescription stimulants include amphetamine, dextroamphetamine, amphetamine mixed salts, lisdexamfetamine, methylphenidate, dexmethylphenidate, and methamphetamine. Regulated pharmaceutical cocaine and stimulants indicated for weight-loss (e.g., phentermine) are not included.

Note: Reports of illicit and regulated pharmaceutical cocaine exposures are considered together.

Note: Amphetamine exposures not referencing a specific prescription product are considered "Amphetamine (NOS)." Note: NMU consists of "Intentional – Misuse" and "Intentional–Abuse" exposures.

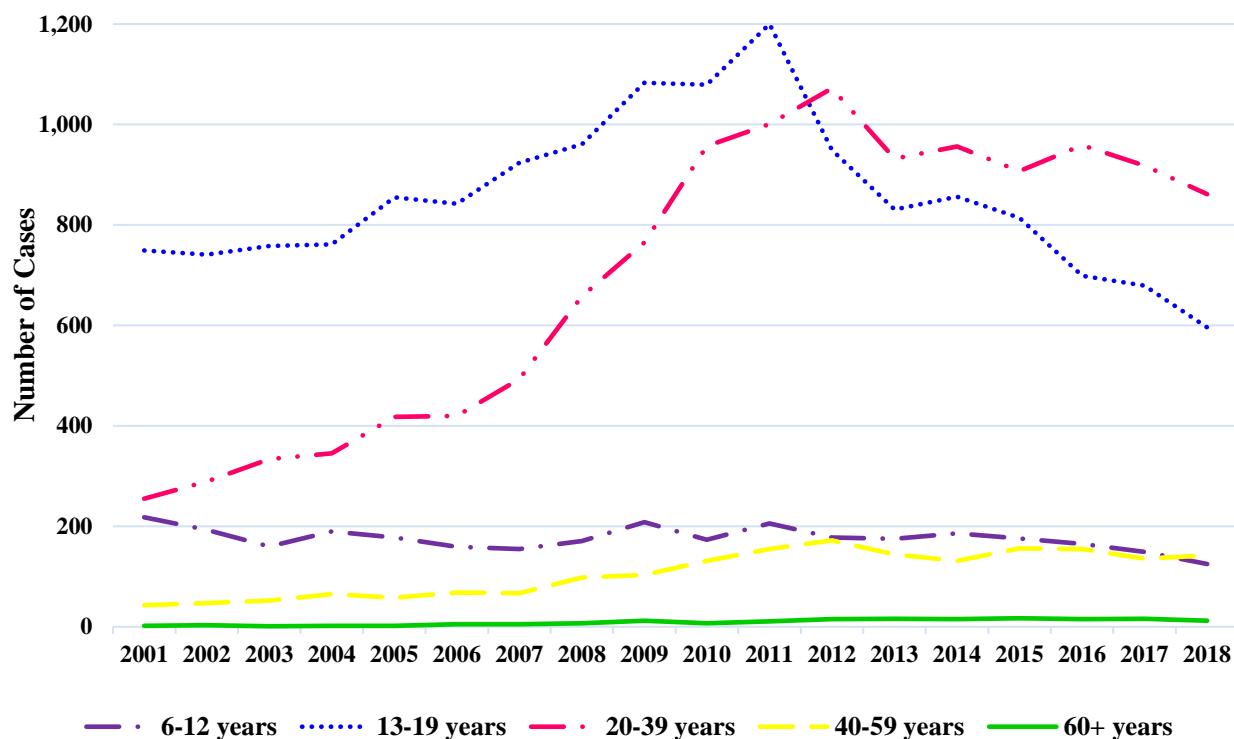
Note: Excludes prescription and illicit stimulant exposure cases with "Intentional–Suspected Suicide" or "Intentional–Unknown" reasons.

Note: Children 5 years and younger (N=187) are not included.

Abbreviations: CII = Schedule II, NMU = nonmedical use, NOS = not otherwise specified

Trends in prescription stimulant NPDS exposure cases from 2001 to 2018 showed that individuals between ages 13 to 19 years and 20 to 39 years had the largest number of NMU cases (i.e., cases categorized as intentional *misuse* or *abuse*) involving prescription stimulants (Figure 12). The number of NMU cases for these age groups peaked between 2011 and 2012 and slightly decreased through 2018. As a comparison, NPDS exposure cases involving NMU of prescription stimulants remained stable over the 18-year period for children less than 12 years of age and for adults greater than 40 years of age.

Figure 12. National Poison Data System Exposure Cases Involving NMU for CII Prescription Stimulants[‡] (Excluding Regulated Pharmaceutical Cocaine), by Year and Age, 2001 to 2018



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

Note: '‡' indicates CII prescription stimulants only. Prescription stimulants include amphetamine, dextroamphetamine, amphetamine mixed salts, lisdexamfetamine, methylphenidate, dexmethylphenidate, and methamphetamine. Regulated pharmaceutical cocaine and stimulants indicated for weight-loss (e.g., phentermine) are not included.

Note: NMU consists of "Intentional–Misuse" and "Intentional–Abuse" exposures.

Note: Excludes prescription stimulant exposure cases with "Intentional–Suspected Suicide" or "Intentional–Unknown" reasons.

Note: Children 5 years and younger (N=90) and exposure cases with missing age (N=1561) are not included.

Abbreviations: CII = Schedule II, NMU = nonmedical use

Prescription Stimulant NMU in Enriched Populations: People Being Assessed for or Entering Treatment for SUD

Adults and adolescents being assessed for substance abuse problems and treatment planning can serve as a valuable source of information for the evaluation of NMU of prescription stimulants. According to data collected from the Treatment Episode Data Set (TEDS), the most common primary drugs used by adolescents and adults admitted to publicly funded treatment programs for assessment and treatment of SUDs in 2017 were opiates¹² (34.0%), with 78% of that being heroin, followed by alcohol (29.5%). Stimulants¹³ accounted for 12.0% of the primary substances reported, with 11.4% of that being methamphetamine. Therefore, stimulants other than methamphetamine collectively accounted for <1% of primary substances used reported in TEDS. Similar patterns were observed in data collected from adults (Addiction Severity Index–Multimedia Version [ASI-MV®]) and adolescents (Comprehensive Health Assessment for Teens [CHAT®]) being assessed for or seeking treatment for SUD, with 1.7% of adults and 4.3% of

¹² Opiates include heroin, non-prescription methadone, and other opiates/synthetics.

¹³ Stimulants include methamphetamine, other amphetamines, and other stimulants. Cocaine is not included in this stimulant group and is listed separately in the dataset.

adolescents reporting NMU of prescription stimulants in the past 30 days. Because study populations drawn from individuals entering treatment facilities are dynamic and nonrepresentative, trends must be interpreted with caution. The Applicant, however, points out that yearly rates of prescription amphetamine past 30-day NMU in adults being assessed for or entering treatment for SUD, as reported in AR19.MA003, increased from approximately 0.8 cases per 100 ASI-MV® assessments in 2010 to 1.7 cases per 100 ASI-MV® assessments in 2017. However, after controlling for the number of prescriptions dispensed, yearly rates of NMU of any prescription amphetamine in the past 30 days appeared to be relatively constant between 2010 and 2017.

9.4.2.2.2. Route of Administration in NMU of Prescription Stimulants

The epidemiologic data reviewed suggest that NMU of CII prescription stimulants primarily occurs via an oral route in the general population; however, a substantial minority of prescription stimulant NMU occurs via non-oral routes, particularly snorting. Some subpopulations more frequently reported non-oral use of prescription stimulants, such as people with more severe substance use problems who are being assessed or treated for SUDs, surveys of individuals with a history of NMU via a non-oral route, and college students who participated in Greek life. The prevalence of different routes reported for NMU of prescription stimulants for the studies reviewed are as follows with bolding to indicate the population or subpopulation:

- Among **adults aged 18 to 49 years** with a lifetime history of NMU of prescription stimulants enrolled in the **general population** survey AR19.MA004, more than 90% of respondents reported lifetime NMU of prescription stimulants via an oral route of administration and 27% reported lifetime NMU of prescription stimulants via at least one non-oral route of administration.
- Among **college-aged** (i.e., 18 to 26 years of age) individuals with lifetime NMU of prescription stimulants, 95.8% of respondents enrolled in college who did not participate in a fraternity/sorority reported NMU of prescription stimulants via an oral route and 15.3% reported a non-oral route, while 88.0% of respondents enrolled in college who **participated in a fraternity/sorority (i.e., Greek life)** reported NMU of prescription stimulants via an oral route and 48.0% reported a non-oral route.
- Among **college-aged** individuals in AR19.MA012 with lifetime NMU of prescription stimulants **not enrolled in college**, 89.8% reported NMU of prescription stimulants via an oral route, while 30.7% reported a non-oral route.
- Among **exposure cases based on calls to PCCs**, 91.4% of exposure route mentions in NPDS cases involving NMU of CII prescription stimulants were oral and 8.6% of exposure route mentions were non-oral (nasal/inhalation or injection).
- Among **adolescents seeking treatment for or being assessed for SUDs** with NMU of prescription stimulants enrolled in AR19.MA003, 83.1% reported NMU via an oral route of administration, while 42.4% reported snorting, 4.8% reported smoking, and 2.5% reported injecting.

- Among **adults seeking treatment for or being assessed for SUDs** with NMU of prescription stimulants enrolled in AR19.MA003, 79.7% reported NMU via an oral route of administration, while 38.8% reported snorting, 3.8% reported smoking, and 12.0% injecting.
- Among **adults with a lifetime history of NMU of prescription stimulants via a non-oral route of administration**, the proportion who reported an oral route of administration varied (AR19.MA008, 85.3%; NOMAD, 70.5%). Among these same adults 99.1% reported snorting, 3.6% reported smoking, and 6.2% reported injecting in AR19.MA008 and 70.3% reported snorting, 26.7% reported smoking, and 20.6% reported injecting in the NOMAD study. Additionally, among **youth ages 10 to 17 years** included in AR19.MA010 with a **history of NMU of prescription stimulants via a non-oral route of administration**, 52% reported oral NMU along with non-oral NMU, while 26% reported only snorting and 15% reported only smoking.

Qualitatively, the patterns pertaining to routes of administration used were similar for NMU of prescription opioid analgesics and NMU of prescription stimulants, with predominantly oral NMU and some non-oral NMU. However, data collected from the **general population** survey AR19.MA004 showed only 11.8% of individuals with lifetime NMU of prescription opioid analgesics reported any non-oral routes of administration compared to 27.2% of individuals with lifetime NMU of prescription stimulants. This difference was largely driven by higher rates of snorting in those reporting NMU of prescription stimulants. *Note: The comparison of routes by prescription stimulant vs opioid analgesic class can be misleading, as the opioid analgesic market largely comprises low-dose IR products in combination with non-opioid analgesics such as acetaminophen.¹⁴ These combination products have relatively low levels of non-oral use, compared to less frequently prescribed single-entity products available in higher dosage strengths. Routes of administration vary greatly by opioid analgesic drug (active ingredient), as described, below, as well as whether the product is single-entity or combined with a non-opioid analgesic (e.g., acetaminophen) (see Supplemental Figure 1A, Cassidy et al., 2017¹⁵).*

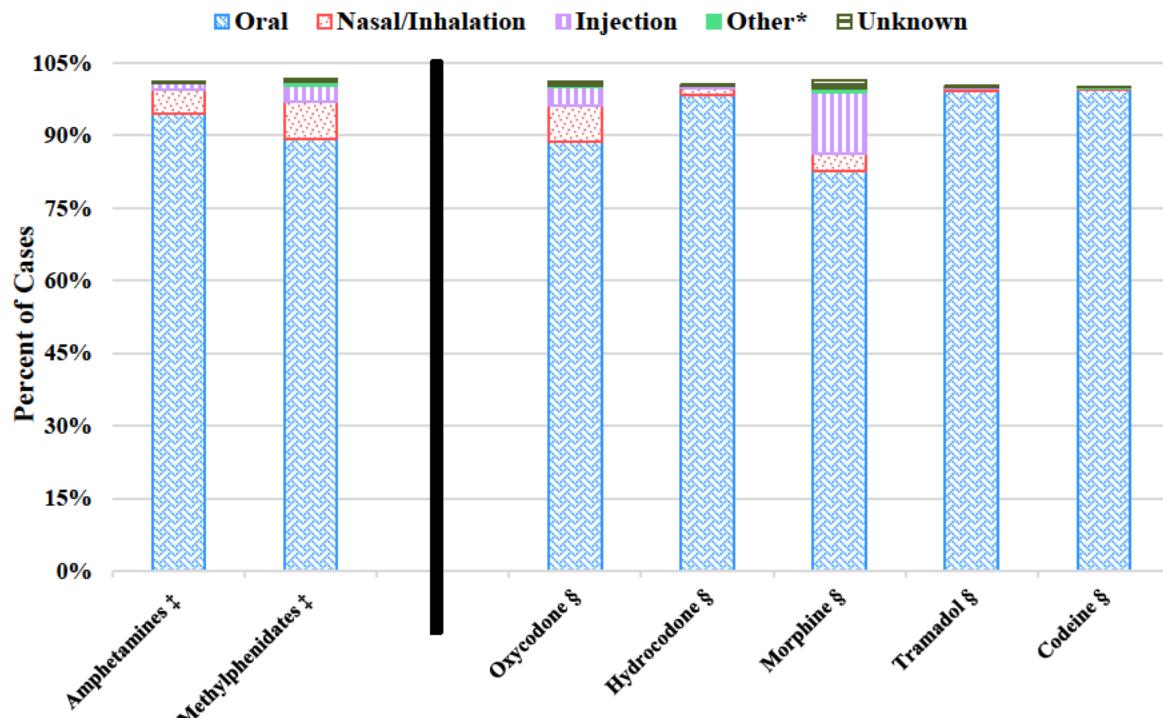
Oral routes of administration were also most common for NPDS exposure cases involving single-substance NMU of prescription amphetamines, methylphenidates, and selected opioid analgesic APIs. For prescription amphetamine and methylphenidate APIs from 2001 to 2018 and for prescription oxycodone, hydrocodone, morphine, tramadol, and codeine APIs from 2014 to 2018, the vast majority (82% to over 99%) of single-substance NMU NPDS cases documented an oral route of exposure (Figure 13). However, there was wider variation in the route of exposure documented for single-substance NMU cases for individual prescription opioid analgesic APIs. As noted above, some of this apparent variation by opioid analgesic API may be related to the heterogeneity of the opioid analgesic market, which includes low-dose IR combination products (e.g., hydrocodone/acetaminophen, oxycodone/acetaminophen) as well as higher dosage strength single-entity and ER products. For IR oxycodone combination products, almost 89% of single-substance NPDS cases, which indicated abuse only, documented an oral exposure route, while over 7% of cases documented snorting and almost 5% documented injection. In comparison, for both single entity, IR oxycodone products and ER oxycodone

¹⁴ <https://www.fda.gov/media/134128/download>

¹⁵ <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5637894/bin/PDS-26-1071-s001.pdf>

products, less than 75% of abuse cases documented an oral exposure route, while over 14% documented snorting and over 12% documented injection.

Figure 13. National Poison Data System Single-Substance Exposure Cases Involving NMU of Prescription Stimulants and Opioid Analgesics, by Route of Exposure



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

Note: ‡ indicates CII prescription stimulants only. Prescription stimulants include amphetamine, dextroamphetamine, amphetamine mixed salts, lisdexamfetamine, methylphenidate, and dexmethylphenidate. Regulated pharmaceutical cocaine and stimulants indicated for weight-loss (e.g., phentermine) are not included.

Note: Includes single-substance prescription stimulant and single-substance prescription opioid exposure cases only.

Note: NMU consists of "Intentional–Misuse" and "Intentional–Abuse" exposures.

Note: Excludes prescription stimulant and opioid exposure cases with "Intentional–Suspected Suicide" and "Intentional–Unknown" reasons.

Note: Routes are represented as percentage of exposure cases reporting a specific route over all single-substance exposure cases for the stimulant or opioid. One exposure case may be associated with more than one exposure route, thus, the total % for each column may exceed 100%.

Note: Children 5 years and younger are excluded from the prescription stimulant exposure cases.

Note: * Route of exposure "Other" includes aspiration, bite/sting, dermal, ocular, other, otic, rectal, and vaginal.

Note: ‡ 2001 to 2018.

Note: § 2014 to 2018. Joint Meeting of Anesthetic and Analgesic Drug Products Advisory Committee (AADPAC) and Drug Safety and Risk Management Advisory Committee (DSaRM). January 15, 2020. Integrated Review of Epidemiology and Drug Utilization. Table 13. Percentage of misuse/abuse, single-substance abuse cases reporting specific exposure routes for tramadol and selected other opioids^A: U.S., NPDS, 2014–2018. Page 33. Available at: <https://www.fda.gov/media/134128/download> (accessed July 10, 2020).

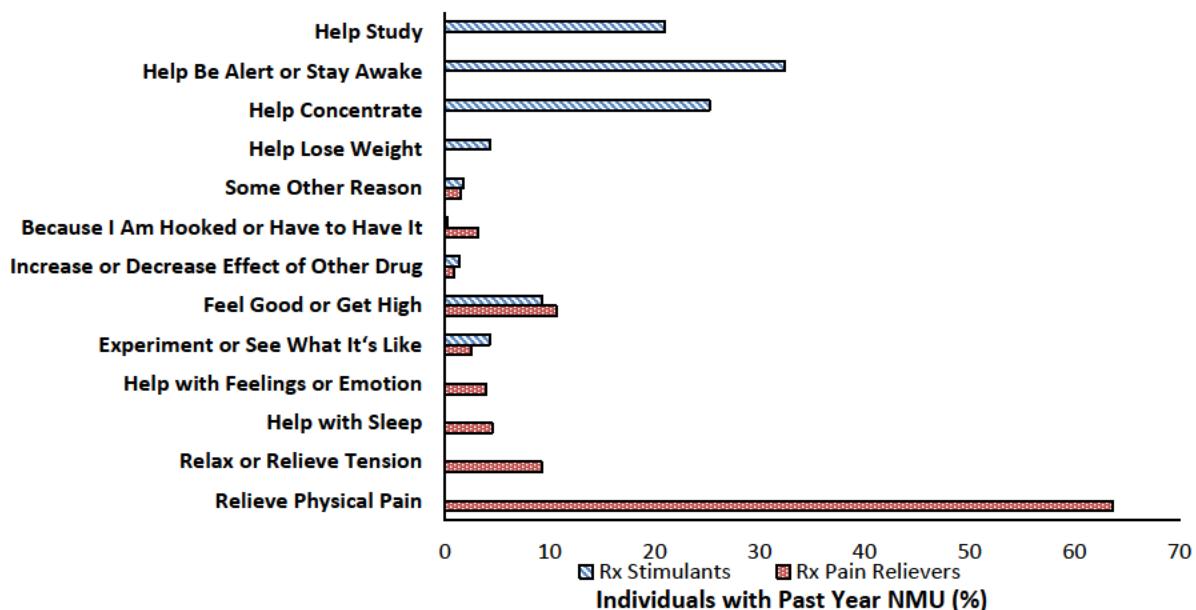
Abbreviations: CII = Schedule II, NMU = nonmedical use

9.4.2.2.3. Reasons/Motivations, Determinants/Risk Factors, and Source of Drugs for NMU of Prescription Stimulants

National surveys of the general population and surveys of college students and adolescents have largely shown the primary motivation for most NMU of prescription stimulants is related to improving performance at work or school, staying alert or awake, or help with concentration, with a minority reporting use to achieve euphoric effects ("to feel good or get high"). In 2018,

data from NSDUH showed that the top three primary reasons individuals age 12 years and older gave for their last prescription stimulant NMU was to help be alert or stay awake, to help concentrate, and to help study, while the top three primary reasons individuals age 12 years and older gave for their last prescription pain reliever NMU was to relieve physical pain, to feel good or get high, and to relax or relieve tension (Figure 14). When compared to individuals with NMU of prescription pain relievers (10.6%), a similar proportion of individuals with NMU of prescription stimulants (9.3%) gave their primary reason as “to feel good or get high.” However, the primary motivations for NMU of prescription stimulants differed in certain subpopulations and with different routes of administration. College students with a history of NMU of prescription stimulants included in AR19.MA012 reported their primary reason as “to enhance performance at work or school” at a higher frequency than what was reported within the general population sample of AR19.MA004 respondents (39.1% versus 28.1%), with the highest frequency observed among college students who also participated in Greek life (56.0%). Among individuals aged 18 to 49 years who reported lifetime NMU of prescription stimulants in the general population survey AR19.MA004, a greater proportion of respondents reported their primary reason for NMU as “to get high” if the NMU was via snorting (30.9%) or injecting (44.4%) routes of administration as compared to respondents who reported NMU via an oral (13.2%) route of administration.

Figure 14. Main Reason for Last Episode of Prescription Psychotherapeutics NMU, among Individuals Aged ≥12 Years with Past-Year NMU, National Survey on Drug Use and Health, 2018



Source: FDA generated figure. Center for Behavioral Health Statistics and Quality. Results from the National Survey on Drug Use and Health, 2018. Retrieved from <https://www.samhsa.gov/data/>.

Note: NMU of prescription use in any way not directed by a doctor, including use without a prescription of one's own; use in greater amounts, more often, or longer than told to take a drug; or use in any other way not directed by a doctor.

Note: Only a subset of reasons applies to each psychostimulant.

Note: Respondents with unknown information for their reason for NMU were excluded from the analysis, including respondents who reported some other reasons but had unknown data in their write-in responses.

Abbreviations: NMU = nonmedical use, Rx = prescription

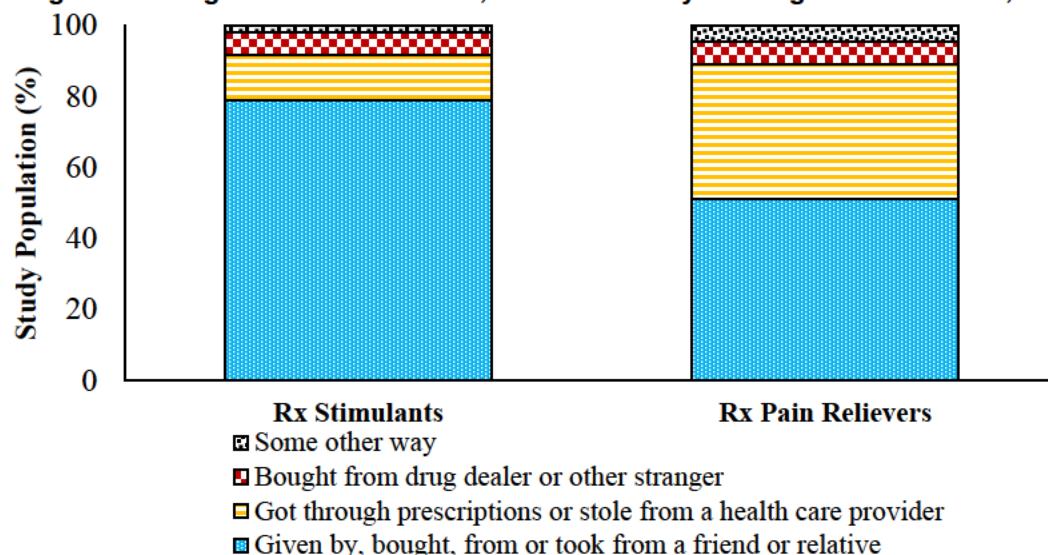
Understanding the determinants and risk factors associated with NMU of prescription stimulants may be valuable in considering the potential benefit of an ADF prescription stimulant product in different patient populations. Although data for the general population are limited, multivariable

analyses conducted on data collected from respondents of AR19.MA004 (an Applicant-submitted online survey of the general U.S. population conducted by the Internet panel company YouGov) suggested that younger age (18 to 25 years); a previous diagnosis of ADHD, conduct disorder, or oppositional defiant disorder; a previous diagnosis of depression, anxiety, or bipolar disorder; and ever use of marijuana, other illicit drugs, or NMU of prescription opioid analgesics were associated with a higher odds of NMU of prescription stimulants. Younger age (18 to 25 years); lifetime diagnosis of a psychiatric disorder, alcohol or SUD, conduct disorder, or oppositional defiant disorder; a 30-day history of binge alcohol use; and lifetime ever use of illicit drugs or NMU of prescription opioid analgesics were associated with higher odds of NMU of prescription stimulants via a non-oral route. A previous diagnosis of ADHD was associated with reduced odds of NMU of a prescription stimulant via a non-oral route.

Because of the potential for diversion of prescription stimulants, gaining a better understanding of how individuals obtain prescription stimulants for NMU can also inform discussion about the potential public health benefits of an ADF prescription stimulant product. According to recent national surveys of the general population and surveys of college students, the most common source of prescription stimulants used nonmedically by individuals aged 12 years and older was friends or relatives. In the 2018 NSDUH data, an estimated 79% of individuals aged 12 years and older identified the source of their last nonmedically used prescription stimulant as “given by, bought from, or took from a friend or relative” ([Figure 15](#)). In AR19.MA010, 71% of youth aged 10 to 17 years reported being given a prescription stimulant for free, and in AR19.MA012, 64% of college students participating in Greek life reported buying, being given, or stealing prescription stimulants from friends or family.

When compared to sources of prescription stimulants used nonmedically, a greater percentage of individuals reported getting prescription pain relievers for NMU from their own prescription or stolen from a healthcare provider. In the 2018 NSDUH data, an estimated 37.6% of individuals aged 12 years or older identified the source of their last nonmedically used prescription pain reliever as “got through prescriptions(s) or stole from health care provider” compared to only 12.8% of individuals with NMU of prescription stimulants ([Figure 15](#)). As a comparison, an estimated 51.3% of individuals aged 12 years or older identified the source of their last nonmedically used prescription pain reliever as “given by, bought from, or took from a friend or relative” compared to 79.1% of individuals with NMU of prescription stimulants.

Figure 15. Source of Prescription Stimulants and Pain Relievers for Most Recent NMU Event, among Persons Aged 12 Years or Older, National Survey on Drug Use and Health, 2018



Source: FDA-generated figure. Center for Behavioral Health Statistics and Quality. Results from the National Survey on Drug Use and Health, 2018. Retrieved from <https://www.samhsa.gov/data/>

Note: NMU of prescription use in any way not directed by a doctor, including use without a prescription of one's own; use in greater amounts, more often, or longer than told to take a drug; or use in any other way not directed by a doctor.

Note: Respondents were asked to choose only one source. Respondents with unknown data on source for most recent NMU and respondents with unknown or invalid responses to the corresponding other-specify questions were excluded from the analysis.

Note: Some Other Way includes write-in responses not already listed in this table or responses with insufficient information that could allow them to be placed in another category.

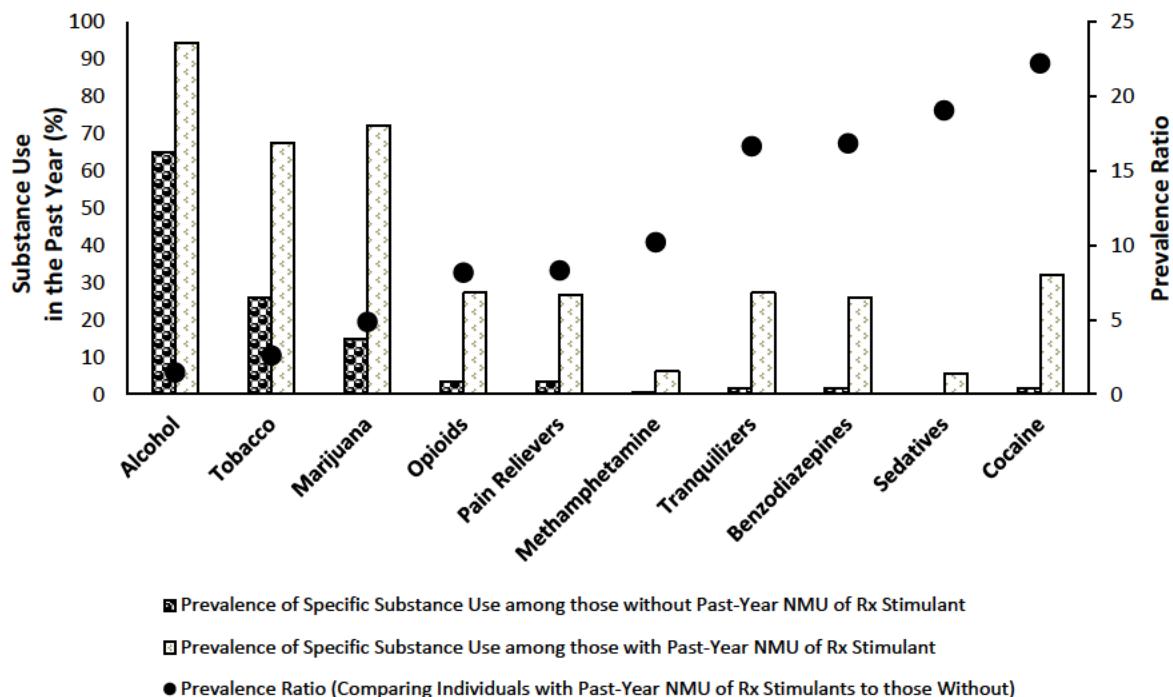
Abbreviations: NMU = nonmedical use, Rx = prescription

9.4.2.2.4. Polysubstance Use and NMU of Prescription Stimulants

Polysubstance use is common among individuals reporting NMU of prescription stimulants. The 2018 NSDUH data showed that within the general U.S. population the most common additional substances used by individuals aged 12 years and older who reported past-year prescription stimulant NMU with other substances were alcohol (94.1%), marijuana (72.1%), and tobacco (67.5%) (Figure 16). Although the prevalence was lower, alcohol, marijuana, and tobacco were also the most commonly reported drugs used among those without stimulant NMU in the past year. Applicant-submitted survey data from AR19.MA004 showed that individuals aged 18 to 49 years with a lifetime history of NMU of prescription stimulants most frequently reported also using caffeine, tobacco, alcohol, and marijuana, similar to the NSDUH data. Compared to individuals who ever nonmedically used a prescription opioid analgesic, individuals who ever nonmedically used a prescription stimulant were more likely to also report use of other substances, especially heroin, methamphetamine, and street fentanyl.

Individuals included in AR19.MA004 who reported non-oral routes of administration for prescription stimulant NMU also reported a higher rate of polysubstance use than those with NMU by the oral route. Individuals reporting NMU of prescription stimulants via snorting or injection were at least twice as likely to report polysubstance use of illicit drugs such as cocaine, heroin, street fentanyl, or methamphetamine, compared to individuals reporting prescription stimulant NMU by the oral route.

Figure 16. NMU of Prescription Stimulants and Polysubstance Use, among Persons Aged 12 Years or Older, National Survey on Drug Use and Health, 2018



Source: FDA-generated figure. Center for Behavioral Health Statistics and Quality. Results from the National Survey on Drug Use and Health, 2018. Retrieved using the crosstab analyses tool made available by the Public-use Data Analysis System provided by SAMHSA <https://www.samhsa.gov/data/>.

Note: NMU (i.e., misuse) of prescription use in any way not directed by a doctor, including use without a prescription of one's own; use in greater amounts, more often, or longer than told to take a drug; or use in any other way not directed by a doctor.

Note: Prevalence ratios for each substance were calculated by taking proportion of individuals with misuse of that substance who also had prescription stimulant misuse in the past year over the proportion of individuals with misuse of that substance who did misuse prescription stimulants in the past year. For example, the prevalence of cocaine use in the past year among individuals who also misused prescription stimulants in the past year was 32.17%, while the prevalence of cocaine use in the past year among individuals without misuse of prescription stimulants in the past year was 1.45%. The prevalence ratio for cocaine was calculated by taking proportion of those two values (i.e., 32.17% divided by 1.45%), which resulted in a prevalence ratio of 22.2 for cocaine.

Abbreviations: NMU = nonmedical use, Rx = prescription

In study AR19.MA012, among adolescents and young adults aged 18 to 26 years with a history of NMU of prescription stimulants, cocaine was the most frequently reported other substance used, followed by caffeine, alcohol, tobacco, and marijuana.

From 2001 through 2018, 36.5% of NPDS exposure cases involving NMU of CII prescription stimulants also involved additional substances, most often alcohol (23.4%), benzodiazepines (19.2%), illicit opioids (16.9%), cannabis (9.0%), cocaine or methamphetamine (6.8%), or muscle relaxants (2.8%). Among ED visits occurring in the United States from 2016 to 2018 related to adverse events involving NMU of CII prescription stimulants in which concurrent substance use was documented, the most commonly documented substances included marijuana, benzodiazepines, alcohol, prescription opioid analgesics, and cocaine.

9.4.2.2.5. Trajectory of Stimulant NMU

Epidemiologic data examining the trajectories of drug use related to prescription stimulants NMU are limited. Most available data are from cross-sectional surveys, rather than longitudinal

studies, and suggest that the pathways involving NMU of prescription stimulants are diverse and often include use of multiple substances.

Data collected from individuals with a history of NMU of prescription ADHD stimulants via a non-oral route (the Applicant-submitted NOMAD survey) indicated that 79.8% of respondents reported some form of substance abuse *prior to* their non-oral abuse of prescription stimulants. Among those who reported prior substance use, marijuana was the most common substance (86.2%), followed by prescription painkillers (36.9%), benzodiazepines (34.7%), and cocaine (27.3%). The majority of respondents (61.5%) also reported oral NMU of prescription stimulants prior to initiating non-oral NMU, while a substantial minority of respondents (20.2%) had no history of substance abuse prior to their non-oral NMU of prescription stimulants.

Similar to the NOMAD survey, data collected from AR19.MA004 suggested that approximately 30% of respondents with NMU of multiple substances, which included prescription stimulants, initiated their NMU pathway with a prescription stimulant. Also, 65.2% of respondents initiated their NMU pathways with an illicit substance, primarily marijuana. The use of illicit substances prior to NMU of prescription stimulants was observed within most cross-sectional surveys included in this section of the FDA briefing document but varied widely in magnitude across studies.

Data from AR19.MA008 suggested that 85.7% of respondents with a history of NMU of prescription stimulants via a non-oral route reported NMU of prescription stimulants via multiple routes. Of those reporting NMU via multiple routes, 89.1% of respondents initiated their NMU of prescription stimulants via the oral route. Of those AR19.MA008 respondents that initiated their NMU of prescription stimulants via a non-oral route, 97.9% initiated their NMU of prescription stimulants via snorting.

9.4.2.2.6. Morbidity and Mortality Associated with NMU of Prescription Stimulants

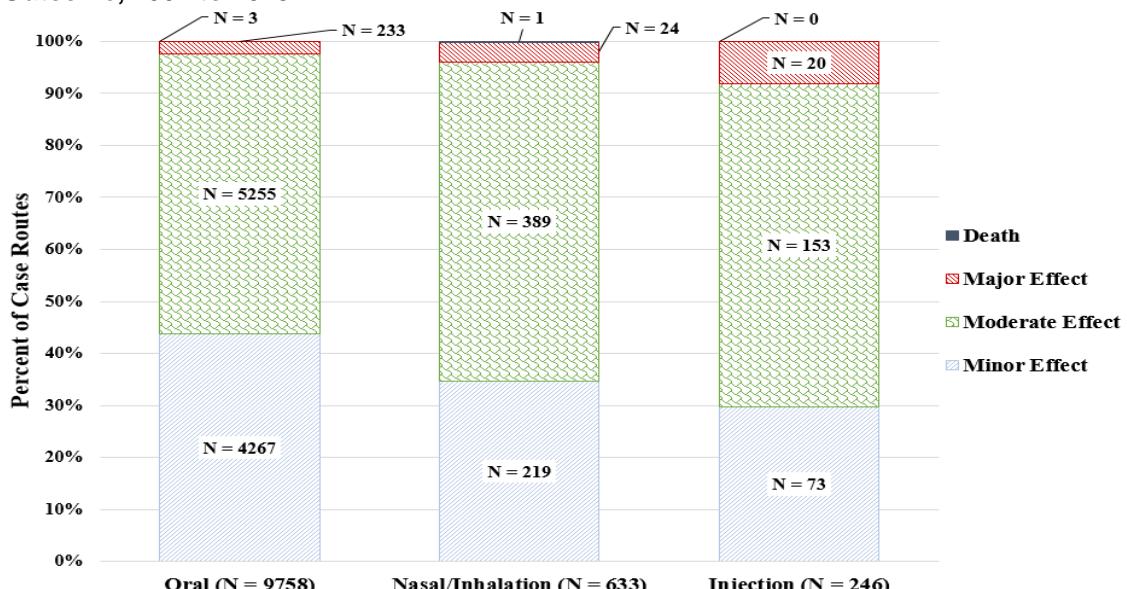
SUDs are an important potential adverse clinical outcome associated with the use and NMU of prescription drugs. NSDUH (2018) estimates that 561,000 people aged 12 years or older had a stimulant use disorder, corresponding to approximately 0.2% of the population. The highest prevalence of stimulant use disorder was among individuals aged 18 to 25 years (estimated at 185,000 individuals), corresponding to 0.5% of the population. In NSDUH, methamphetamine and cocaine are not included in the stimulant use disorder statistic; methamphetamine and cocaine use disorders are considered separately.

Information collected from NPDS cases provide an additional source of information on the harms associated with NMU of prescription stimulants. From 2001 to 2018, over 95% of NPDS exposure cases for single-substance NMU of CII prescription stimulants documented either a minor or moderate effect as a result of the exposure, with 45% of cases documenting only minor effects resulting from the exposure, and less than 3% of cases documenting major effects from the exposure. In general, the proportion of cases with major effects for other stimulant categories (e.g., cocaine, methamphetamine) was higher compared to that for prescription stimulants. It is important to note, however, that NPDS generally does not capture unattended and out-of-hospital deaths. The top three related clinical outcomes documented for single-substance prescription

stimulant NMU exposure cases that had a medical outcome related to the exposure were tachycardia, agitation, and hypertension.

The adverse health outcomes associated with NMU of prescription stimulants varied by the NMU route of administration in NPDS data. Among single-substance NMU exposure cases that involved CII prescription stimulants, approximately 70% of injection route mentions had a related medical outcome with a moderate or major effect, while approximately 65% of nasal/inhalation and approximately 56% of oral route mentions had a related medical outcome with a moderate or major effect (Figure 17).¹⁶ Although moderate or major health effects were documented in a greater proportion of cases that mentioned injection or nasal/inhalation routes compared to oral routes, almost 90% of the total route mentions with more severe medical outcomes (moderate and major effects) were in cases reporting an oral route of exposure.

Figure 17. National Poison Data System Single-Substance Exposure Cases Involving NMU of CII Prescription Stimulants[‡] (excluding regulated pharmaceutical cocaine), by Route and Medical Outcome, 2001 to 2018



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

Note: '[‡]' indicates CII stimulants only. Prescription stimulants include amphetamine, dextroamphetamine, amphetamine mixed salts, lisdexamfetamine, methylphenidate, dextroamphetamine, and methamphetamine. Regulated pharmaceutical cocaine and stimulants indicated for weight-loss (e.g., phentermine) are not included.

Note: Includes single-substance, related medical outcome prescription stimulant exposure cases only.

Note: NMU consists of "Intentional-Misuse" and "Intentional-Abuse" exposures.

Note: Excludes prescription stimulant exposure cases with "Intentional-Suspected Suicide" or "Intentional-Unknown" reasons.

Note: Excludes prescription stimulant exposure cases with Medical Outcomes "Not/Unable to Follow" (N=3,888) and "Unrelated Effect" (N=7).

Note: Total route of exposure mentions for the routes "Other-aspiration, bite/sting, dermal, ocular, other, otic, rectal, and vaginal" (N=40) and "Unknown" (N=21) are not included in this figure.

Note: Children 5 years and younger are not included.

Note: Routes are represented as percentage of total route of misuse/abuse mentions for prescription stimulants.

Abbreviations: CII = Schedule II, NMU = nonmedical use

Among U.S. ED visits due to adverse events involving NMU of CII prescription stimulants from 2016 through 2018, cardiovascular effects were the most common clinical manifestations;

¹⁶ Multiple routes can be mentioned during one case, so we considered differences in adverse health outcomes by route mention.

followed by presyncope, syncope, or dyspnea; altered mental status; and neuropsychiatric effects. Cardiovascular effects were also some of the most commonly documented clinical manifestations/outcomes related to NMU of prescription stimulants in NPDS exposure cases, as discussed above.

We also analyzed U.S. ED visits to provide annual estimates of the number of visits for harms related to NMU of CII prescription stimulants relative to visits for harms related to NMU of prescription opioid analgesics. In 2016, approximately 11,000 U.S. ED visits (around 3% of total visits related to NMU of pharmaceuticals) were estimated to have involved NMU of CII prescription stimulants with or without other substances, whereas approximately 130,000 visits (around 36% of total visits related to NMU of pharmaceuticals) were estimated to have involved NMU of prescription opioid analgesics with or without other substances (Geller et al. 2019). When U.S. ED visits in 2016 were restricted to single-substance-only visits related to NMU of pharmaceuticals, an estimated 3,677 annual visits (1.0% of total visits related to NMU of pharmaceuticals) involved NMU of only CII prescription stimulants, while an estimated 40,499 annual visits (11.3% of total visits related to NMU of pharmaceuticals) involved NMU of only prescription opioid analgesics.

The FAERS database provides qualitative information on morbidity and mortality associated with NMU of prescription stimulants. Between 2007 and 2020, we identified 92 U.S. FAERS cases of NMU of CII prescription stimulants via a non-oral route, including 31 U.S. cases reporting a fatal outcome. The top reported non-oral routes of nonmedical CII prescription stimulant use in the U.S. were snorting (n=38), followed by inhalation¹⁷ (n=32) and injection (n=25), although there were substantially more FAERS reports of nonmedical CII prescription stimulant use via the oral route (n=5,680) compared to non-oral routes from January 1, 2007, through April 23, 2020. From 2007 through 2016, the most commonly reported CII prescription stimulant nonmedically used via the non-oral route was methylphenidate; however, since 2017, more than half of recent U.S. FAERS reports for NMU of stimulants via a non-oral route involved methamphetamine, which was likely illicit methamphetamine based on the extremely low sales volume of prescription methamphetamine. Approximately 36% of U.S. prescription stimulant non-oral NMU FAERS cases reported CII prescription stimulant use without use of any other substances.

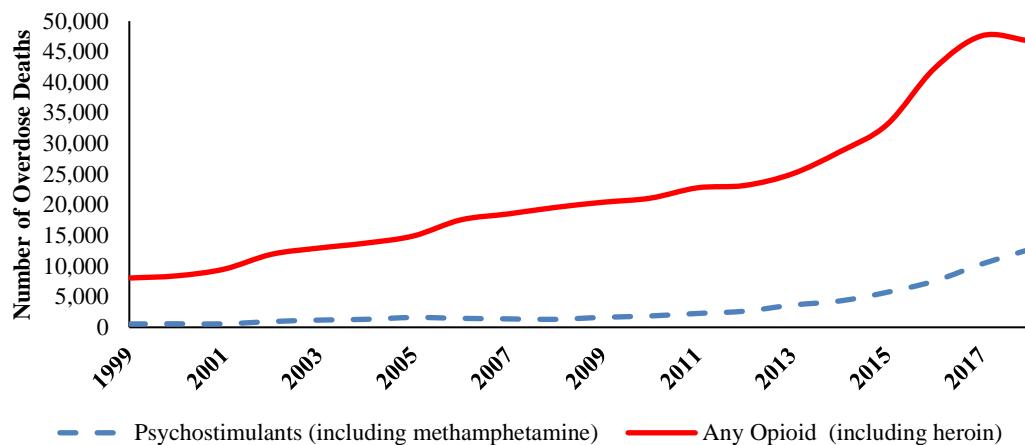
Adverse reactions reported in the medical literature that were associated with NMU of CII prescription stimulants by any route include cardiovascular, cerebrovascular, psychiatric and behavioral, unintentional and intentional injury, infectious disease, and pulmonary reactions, many of which are potentially life threatening. The top five System Organ Classes for the adverse events most frequently reported in FAERS with nonmedical CII prescription stimulant use via non-oral routes were *psychiatric disorders; injury, poisoning and procedural complications; general disorders and administration site conditions; respiratory, thoracic and mediastinal disorders; and nervous system disorders*. Overall, in the United States from 2007 to 2020, 77% of cases with nonmedical CII prescription stimulant use via a non-oral route reported one or more adverse events, although most of the adverse events reported with nonmedical CII prescription stimulant use via non-oral routes were labeled events for the stimulant products or were events associated with drug dependence. Unlabeled adverse events reported with inhalation

¹⁷ Inhalation includes smoking and inhalation not further defined.

of CII prescription stimulants included pulmonary toxicity, epistaxis, and pulmonary edema, while those reported with injection of CII prescription stimulants included injection site edema, endocarditis, hepatitis A, and hepatitis C.

Overdose death involving prescription stimulants is another important adverse outcome to consider. [Figure 18](#) shows that overdose deaths involving opioids and those involving psychostimulant drugs increased from 1999 to 2018 in the United States, with greater increases in psychostimulant overdose deaths beginning around 2011. However, as of 2018, the number of psychostimulant overdose deaths remained much lower than the number of opioid overdose deaths. An important note is that these data group CII prescription stimulants under the same International Classification of Diseases, Tenth Edition (ICD-10) code as other stimulants, including methamphetamine and other illicit stimulant drugs, such as ecstasy (T43.6: psychostimulants with abuse potential). The category of all opioid overdose deaths also includes illicit opioids such as heroin and illicit fentanyl.

Figure 18. Annual Number of Overdose Deaths in the United States Involving Psychostimulants and Opioids, National Vital Statistics System Multiple Cause of Death Database, 1999 to 2018



Source: FDA-generated figure. Data Brief 356. Drug Overdose Deaths in the United States, 1999–2018. Accessed from https://www.cdc.gov/nchs/data/databriefs/db356_tables-508.pdf#3.

Notes: Drug overdose deaths are identified using International Classification of Diseases, Tenth Revision underlying cause-of-death codes X40–X44, X60–X64, X85, and Y10–Y14. Drug overdose deaths involving selected drug categories are identified by specific multiple-cause-of-death codes: “Opioids” include heroin (T40.1); natural and semisynthetic opioids (T40.2); methadone (T40.3); and synthetic opioids excluding methadone (T40.4); “Psychostimulants” refers to psychostimulants with abuse potential (T43.6). Psychostimulants with abuse potential include such drugs as methamphetamine, amphetamine, methylphenidate.

Because of the noted limitations related to limited differentiation of prescription stimulants from publicly available mortality data, we supplemented the above analysis with national data on stimulant-involved mortality using death certificate literal text, made available to the Agency by the National Center for Health Statistics. An updated analysis of these data was not possible at the time of this review as we were unable to access the National Center for Health Statistics’ Research Data Center due to restrictions associated with the ongoing SARS-CoV-2 pandemic. Based on available data from 2010 through 2014, methamphetamine was involved in the largest number of stimulant-involved deaths (19,268 decedents) of U.S. residents, followed by amphetamine (3,493 decedents), although it is unclear what proportion of amphetamine deaths specifically involved a CII stimulant containing amphetamine salts and what proportion refers to the general amphetamine class of drugs ([Table 7](#)). Of note, published analyses indicate that the reporting of at least one specific drug in the death certificate literal text has improved during the

study period ([Warner et al. 2016](#)), so there may be some contribution to increasing trends over time from better reporting of specific drugs in death certificates.

Table 7. Number of Deaths Involving Selected Stimulants, among U.S. Residents, 2010 to 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

Source: FDA analysis of NCHS, National Vital Statistics System, Mortality files linked with death certificate literal text. Constructed for analysis on October 6, 2016.

Note: Deaths involving more than one drug (e.g., a death involving both methamphetamine and amphetamine) are counted in totals for each drug.

Abbreviation: U.S. = United States

Other than methamphetamine (most likely illicit), amphetamine was the only other stimulant API in the top 15 drugs mentioned on overdose death certificates from 2011 to 2016 and was documented as being involved in 1.9% of overdose deaths, whereas opioid analgesic APIs were frequently in the top 15 drugs.¹⁸ However, it is important to note that these comparisons do not account for differences in prescription volume for these products. Overall, 2016 death certificate mentions show that fentanyl, heroin, and cocaine were the top three drugs involved in drug overdose deaths.

9.4.3. Data Strengths and Limitations

1. Drug Utilization

The drug utilization databases used in this section of FDA's briefing document have many strengths. First, the databases account for approximately 92% of retail prescriptions dispensed nationwide. Second, the databases span multiple years and include API-specific data, including information on IR/ER products, as well as dosage strengths. Third, the databases provide some limited information on patient demographics, such as age. The databases also have limitations. For example, dispensing patterns were limited to the outpatient retail setting and information on utilization of illicit stimulants and other nonprescription medications was not accessible.

2. Pharmacovigilance

The strength of FAERS data is the inclusion of all marketed products, uses (approved indications and off-label uses), and patient populations. FAERS data are especially useful for capturing rare events and events that occur shortly after exposure. However, FAERS data do have some notable limitations. FDA does not require that a causal relationship between a

¹⁸ National Center for Health Statistics, National Vital Statistics System, Mortality files linked with death certificate literal text, 2011-2016. https://www.cdc.gov/nchs/data/nvsr/nvsr67/nvsr67_09-508.pdf (accessed 8.25.2020)

product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, the data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.

3. FDA and Applicant-Submitted Epidemiologic Data on NMU

Cross-sectional epidemiologic surveys provided detailed information on NMU patterns and outcomes associated with prescription stimulants. These studies were designed to emulate the general population (e.g., NSDUH, MTF, and AR19.MA004) or targeted for specific populations of interest, such as college students (e.g., AR19.MA012), youth in the community (AR19.MA008), or individuals with a history of non-oral prescription stimulant use (e.g., AR19.MA008, NOMAD). The validity of the results for certain surveys was strengthened by the use of well-established sampling and survey methodology (e.g., NSDUH, MTF). However, many of these cross-sectional surveys also possessed notable limitations. For instance, selection bias may have occurred to varying degrees across surveys, particularly those not using probability sampling methods (i.e., representative samples). Misclassification of exposure may have also occurred and been complicated further by the use of different windows of exposure (e.g., lifetime use, past-year use) and lack of validation of survey questions. The use of cross-sectional surveys to assess temporal relationships between past events (e.g., NOMAD, AR19.MA008) also introduces the potential for recall and confirmation bias, which need to be considered in interpreting results.

Data collected from NPDS exposure cases in the United States provided detailed information on specific products, reasons for use, route of administration, and medical outcomes. While not necessarily representative of all NMU or all adverse events associated with NMU in the U.S. population, NPDS exposure cases are captured nationwide. Data collected from PCC calls and uploaded to NPDS have limitations. The cases are subject to errors from self-reported data, and the level of completeness of the information varies among cases. Not all cases are followed to final medical outcomes and deaths are likely vastly underestimated in the data. Finally, the proportion of cases captured in NPDS can vary over time and across drugs.

Data collected from ED visits (National Electronic Injury Surveillance System–Cooperative Adverse Drug Event Surveillance [NEISS-CADES]) provided detailed information on the potential harms associated with NMU of prescription stimulants. The data collected were nationally representative, which allowed national estimates of ED visits due to pharmaceutical products to be generated. An important limitation of these data was that information provided in medical charts is not uniform and can vary across medical systems. Additionally, patients may be unable or unwilling to provide details about which substances they took and why they took them, or they may state an inaccurate reason for drug use (e.g., state a therapeutic intent after NMU). This can lead to potential misclassification of exposures and reasons for exposure. Finally, many of the visits included in these data are associated with acute harms resulting in an ED visit and the data do not capture cases in

which care was sought in a non-ED setting, or that resulted in death before or during the ED visit evaluation.

Treatment center data (e.g., ASI-MV[®], CHAT[®], TEDS) provided product-specific information on drugs of abuse leading to treatment assessment/entry. Because assessment is integrated into clinical care, the participation rate is high. Treatment center populations are also enriched for individuals with advanced substance use problems and using alternate routes of administration. Treatment center data are limited by the fact they represent a nonrepresentative, dynamic population sample. Centers enter and leave ASI-MV[®] and CHAT[®] samples over time, which can especially influence the trends for drugs whose NMU patterns vary by geographic region or treatment setting. Furthermore, the generalizability of this population can be difficult to assess, because outside factors (e.g., treatment program capacity, judicial practices) may influence the number and mix of individuals included in the data system at a given time. Treatment center data also rely on self-reported drug abuse behaviors, which can be subject to varying levels of misclassification.

Mortality data collected through national systems, such as the National Vital Statistics System (NVSS-M) and National Data on Drug-Involved Mortality (DIM), are important for our understanding of the overdose potential of prescription stimulants. A major strength of these data is that they capture all deaths in the United States. In the case of DIM, information on the API documented in the literal text of the death certificate was also captured.

Interpreting the precise contribution of prescription stimulants to mortality from these data is hampered by the fact that overdose deaths often involve multiple substances. Furthermore, the data are only available at the API-level, and route and formulation are not often known. It is also important to note that most ICD-10 codes used in NVSS-M capture large groups of drugs, which can obscure the patterns for a drug of interest. Lastly, reporting of at least one specific drug in the death certificate literal text has improved during the study period ([Warner et al. 2016](#)), so there may be some contribution to increasing trends over time from better reporting of specific drugs in death certificates.

9.4.4. Summary of Postmarketing Data

CII prescription stimulants are widely used in the United States for the treatment of ADHD. The number of CII stimulant prescriptions dispensed from U.S. outpatient retail pharmacies has increased from 2008 through 2019, driven by an increase in utilization of mixed amphetamine salt products. Compared to other prescription stimulant products, IR racemic amphetamine sulfate, such as the product under consideration, accounted for only around 0.3% of the overall stimulant market. When compared to prescription opioid analgesics, the national estimate of the number of prescription stimulants dispensed from U.S. outpatient retail pharmacies was approximately half that of prescription opioid analgesics.

NMU of CII prescription stimulants is a serious public health concern but does not reach the magnitude of NMU of some other prescription drug classes, particularly opioid analgesics, which currently are the only drug class with products labeled as abuse-deterrent. The overall prevalence of past-year NMU of prescription stimulants in the general U.S. population in 2018 was approximately 2%, or 5.1 million individuals. In 2018, the prevalence of CII prescription

stimulant NMU was roughly half the prevalence of prescription opioid analgesic NMU; however, among those reporting past-year NMU, the proportion reporting misusing the medications was higher for prescription stimulants than for prescription opioid analgesics. NMU of prescription stimulants is concentrated in young adults ages 21 to 25 years and appears to occur more frequently in individuals diagnosed with ADHD; however, the magnitude of NMU of prescription stimulants has remained relatively stable from 2010 through 2018.

The primary motivation for most NMU of prescription stimulants is related to improving performance at work or school, staying alert or awake, or helping with concentration, with a minority reporting use to achieve euphoric effects (“to feel good or get high”). Individuals who use prescription stimulants nonmedically most frequently reported getting the medication from friends or relatives. This differed from the most common source of prescription pain relievers which was from their own prescription or stolen from a healthcare provider.

Across all data sources, the vast majority of NMU by individuals who use prescription stimulants nonmedically report using them by the oral route. NMU of prescription stimulants via smoking and injection is uncommon in the general population, although a substantial minority of individuals who use prescription stimulants nonmedically report having snorted them. The frequency of using non-oral routes varied considerably by subpopulation and source of the data. Non-oral use of prescription stimulants was more frequent in individuals seeking treatment or being assessed for SUDs, individuals with a history of NMU of prescription stimulants via a non-oral route, and college studies who participated in Greek life. Oral and non-oral routes of administration for NMU of prescription opioid analgesics followed a similar pattern as for NMU of prescription stimulants, although snorting was more common with NMU of prescription stimulants as compared to NMU of prescription opioid analgesics, as a class. However, combination opioid analgesics with non-opioid analgesics, such as acetaminophen, are less commonly snorted than are single-entity products yet are the most common opioid analgesics dispensed, making comparison between the overall proportions of NMU via snorting for prescription stimulants and opioid analgesics as a class potentially misleading. Polysubstance use was common with prescription stimulant NMU, in general, and was even more common in individuals reporting non-oral prescription stimulant NMU when compared to those reporting only oral NMU.

A number of adverse events are associated with NMU of prescription stimulants; however, in NPDS cases based on calls to U.S. PCCs, only a small proportion of adverse events related to NMU of prescription stimulants were more severe. Although more severe related medical outcomes were more frequent with injection or nasal/inhalation routes compared to oral routes, oral NMU contributed to the greatest number of cases with severe medical outcomes, as the vast majority of individuals who used prescription stimulants nonmedically report an oral route of NMU. Overdose deaths involving psychostimulants, such as methamphetamine and other amphetamines, have increased; however, available data from 2010 through 2014 showed that the majority of stimulant overdose deaths mentioned methamphetamine on the death certificate, a minority mentioned amphetamines (which may include illicit methamphetamine), and there were very few mentions of other stimulant APIs.

The potential broader public health effects of AR19 or other ADF stimulant products that deter non-oral use are currently unknown. Based on our experience with ADF opioid analgesics, when assessing the potential public health risks and benefits of ADF products, considerations include:

- Existing patterns of routes of NMU administration
- The severity of adverse events associated with alternate routes of administration
- The bioavailability of the drug by different routes
- The potential for differential impacts across different populations
- Polysubstance use patterns and availability of other substitutable substances
- Possible excipient-related adverse events

It is unlikely that the product under consideration would have a meaningful public health benefit on its own, given the low market share of IR racemic amphetamine sulfate products. In addition, the broader potential public health benefit of ADF stimulant products remains unknown, considering the predominant route of NMU for these products being oral, the high prevalence of polysubstance use, and the availability of both pharmaceutical and illicit substitutes, and the potential excipient harms. The Applicant has proposed to monitor for harms in the postmarket setting related to injecting the excipients in their product, but the low market share of existing racemic amphetamine sulfate products—and the few data sources that can capture product-specific exposure—will likely make it challenging, if not infeasible, to evaluate the magnitude of these and other potential harms as well as benefits in the postmarket setting.

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11. ATTACHMENTS

1. Abuse and Dependence Labeling
2. Guidance for Industry: Abuse-Deterrent Opioids—Evaluation and Labeling
3. General Principles for Evaluating the Abuse Deterrence of Generic Solid Oral Opioid Drug Products
4. Office of Surveillance and Epidemiology Expanded Methods and Results for Postmarketing Data on Stimulant Use and Nonmedical Use

11.1. Abuse and Dependence Labeling

11.1.1. Prescription Stimulants

Labeling of abuse risks varies considerably across prescription stimulants. Below are *excerpts* from Evekeo orally disintegrating tablets (ODT) and Adderall XR. In addition, there are two approved products with human abuse potential study results reported in the label comparing their product to the abuse potential of other approved products (Vyvanse and Concerta). The Agency did not consider these to be abuse-deterrent formulations; however, descriptions of the manufacturers' HAP studies are included in the labels of Vyvanse and Concerta.

EVEKEO ODT

WARNING: ABUSE AND DEPENDENCE

CNS stimulants, including EVEKEO ODT, other amphetamine-containing products, and methylphenidate, have a high potential for abuse and dependence. Assess the risk of abuse prior to prescribing and monitor for signs of abuse and dependence while on therapy [see Warnings and Precautions (5.1), and Drug Abuse and Dependence (9.2, 9.3)].

Drug Abuse And Dependence

Evekeo ODT is a CNS stimulant that contains amphetamine which has a high potential for abuse. Abuse is characterized by impaired control over drug use, compulsive use, continued use despite harm, and craving. Signs and symptoms of amphetamine abuse may include increased heart rate, respiratory rate, blood pressure, and/or sweating, dilated pupils, hyperactivity, restlessness, insomnia, decreased appetite, loss of coordination, tremors, flushed skin, vomiting, and/or abdominal pain. Anxiety, psychosis, hostility, aggression, suicidal or homicidal ideation have also been seen. Abusers of amphetamine may use unapproved routes of administration which can result in overdose and death [see Overdosage (10)].

To reduce the abuse of CNS stimulants, including Evekeo ODT, assess the risk of abuse prior to prescribing. After prescribing, keep careful prescription records, educate patients and their families about abuse and on proper storage and disposal of CNS stimulants. Monitor for signs of abuse while on therapy, and re-evaluate the need for Evekeo ODT use.

ADDERALL XR

WARNING: ABUSE AND DEPENDENCE

See full prescribing information for complete boxed warning

- CNS stimulants, including ADDERALL XR, other amphetamine-containing products, and methylphenidate, have a high potential for abuse and dependence (5.1, 9.3)
- Assess the risk of abuse prior to prescribing and monitor for signs of abuse and dependence while on therapy (9.2, 9.3).

Drug Abuse And Dependence

ADDERALL XR is a CNS stimulant that contains amphetamine, which has a high potential for abuse. Abuse is characterized by impaired control of drug use, compulsive use despite harm, and craving. Signs and symptoms of amphetamine abuse may include increased heart rate, respiratory rate, blood pressure, and/or sweating, dilated pupils, hyperactivity, restlessness, insomnia, decreased appetite, loss of coordination, tremors, flushed skin, vomiting, and/or abdominal pain. Anxiety, psychosis, hostility, aggression, suicidal or homicidal ideation have also been observed. Abusers of amphetamines may use other unapproved routes of administration which can result in overdose and death [see Overdosage (10)]. To reduce the abuse of CNS stimulants, including ADDERALL XR, assess the risk of abuse prior to prescribing. After prescribing, keep careful prescription records, educate patients and their families about abuse and proper storage and disposal of CNS stimulants. Monitor for signs of abuse while on therapy and re-evaluate the need for ADDERALL XR use.

VYVANSE

WARNING: ABUSE AND DEPENDENCE

See full prescribing information for complete boxed warning.

- CNS stimulants (amphetamines and methylphenidate-containing products), including VYVANSE, have a high potential for abuse and dependence (5.1, 9.2, 9.3)
- Assess the risk of abuse prior to prescribing and monitor for signs of abuse and dependence while on therapy (5.1, 9.2)

Drug Abuse And Dependence

CNS stimulants, including VYVANSE, other amphetamines, and methylphenidate-containing products have a high potential for abuse. Abuse is characterized by impaired control over drug use, compulsive use, continued use despite harm, and craving.

Signs and symptoms of CNS stimulant abuse may include increased heart rate, respiratory rate, blood pressure, and/or sweating, dilated pupils, hyperactivity, restlessness, insomnia, decreased appetite, loss of coordination, tremors, flushed skin, vomiting, and/or abdominal pain. Anxiety, psychosis, hostility, aggression, suicidal or homicidal ideation have also been seen. Abusers of CNS stimulants may chew, snort, inject, or use other unapproved routes of administration which can result in overdose and death [*see Overdosage (10)*].

To reduce the abuse of CNS stimulants, including VYVANSE, assess the risk of abuse prior to prescribing. After prescribing, keep careful prescription records, educate patients and their families about abuse and on proper storage and disposal of CNS stimulants, monitor for signs of abuse while on therapy, and re-evaluate the need for VYVANSE use.

Studies of VYVANSE in Drug Abusers:

A randomized, double-blind, placebo-control, cross-over, abuse liability study in 38 patients with a history of drug abuse was conducted with single-doses of 50, 100, or 150 mg of VYVANSE, 40 mg of IR d-amphetamine sulphate (a controlled II substance), and 200 mg of diethylpropion hydrochloride (a controlled IV substance). VYVANSE 100 mg produced significantly less "Drug Liking Effects" as measured by the Drug Rating Questionnaire-Subject score, compared to d-amphetamine 40 mg; and 150 mg of VYVANSE demonstrated similar "Drug-Liking Effects" compared to 40 mg of d-amphetamine and 200 mg of diethylpropion.

Intravenous administration of 50 mg lisdexamfetamine dimesylate to individuals with a history of drug abuse produced positive subjective responses on scales measuring "Drug Liking", "Euphoria", "Amphetamine Effects", and "Benzedrine Effects" that were greater than placebo but less than those produced by an equivalent dose (20 mg) of intravenous d-amphetamine.

CONCERTA

WARNING: DRUG DEPENDENCE

See full prescribing information for complete boxed warning.

CONCERTA® should be given cautiously to patients with a history of drug dependence or alcoholism. Chronic abusive use can lead to marked tolerance and psychological dependence, with varying degrees of abnormal behavior.

Drug Abuse And Dependence

As noted in the Box Warning, CONCERTA® should be given cautiously to patients with a history of drug dependence or alcoholism. Chronic abusive use can lead to marked tolerance and psychological dependence with varying degrees of abnormal behavior. Frank psychotic episodes can occur, especially with parenteral abuse.

In two placebo-controlled human abuse potential studies, single oral doses of CONCERTA® were compared to single oral doses of immediate-release methylphenidate (IR MPH) and placebo in subjects with a history of recreational stimulant use to assess relative abuse potential. For the purpose of this assessment, the response for each of the subjective measures was defined as the maximum effect within the first 8 hours after dose administration.

In one study (n=40), both CONCERTA® (108 mg) and 60 mg IR MPH compared to placebo produced statistically significantly greater responses on the five subjective measures suggestive of abuse potential. In comparisons between the two active treatments, however, CONCERTA® (108 mg) produced variable responses on positive subjective measures that were either statistically indistinguishable from (Abuse Potential, Drug Liking, Amphetamine, and Morphine Benzedrine Group [Euphoria]) or statistically less than (Stimulation – Euphoria) responses produced by 60 mg IR MPH.

In another study (n=49), both doses of CONCERTA® (54 mg and 108 mg) and both doses of IR MPH (50 mg and 90 mg) produced statistically significantly greater responses compared to placebo on the two primary scales used in the study (Drug Liking, Euphoria). When doses of CONCERTA® (54 mg and 108 mg) were compared to IR MPH (50 mg and 90 mg), respectively, CONCERTA® produced statistically significantly lower subjective responses on these two scales than IR MPH. CONCERTA® (108 mg) produced responses that were statistically indistinguishable from the responses on these two scales produced by IR MPH (50 mg). Differences in subjective responses to the respective doses should be considered in the context that only 22% of the total amount of methylphenidate in CONCERTA® tablets is available for immediate release from the drug overcoat [see System Components and Performance (11.1)].

Although these findings reveal a relatively lower response to CONCERTA® on subjective measures suggestive of abuse potential compared to IR MPH at roughly equivalent total MPH doses, the relevance of these findings to the abuse potential of CONCERTA® in the community is unknown.

11.1.2. Prescription Opioid Analgesics

Prescription opioid analgesics represent the only class, to date, that has formulations with labeling that they are expected to deter abuse via certain routes of administration. For this reason, we included an *excerpt* of the abuse labeling for OxyContin, an ER oxycodone formulation with abuse-deterrent labeling, as an example.

OXYCONTIN

WARNING: ADDICTION, ABUSE AND MISUSE; RISK EVALUATION AND MITIGATION STRATEGY (REMS); LIFE-THREATENING RESPIRATORY DEPRESSION; ACCIDENTAL INGESTION; NEONATAL OPIOID WITHDRAWAL SYNDROME; CYTOCHROME P450 3A4 INTERACTION; and RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS

See full prescribing information for complete boxed warning.

- OXYCONTIN exposes users to risks of addiction, abuse and misuse, which can lead to overdose and death. Assess patient's risk before prescribing and monitor regularly for these behaviors and conditions. (5.1)
- To ensure that the benefits of opioid analgesics outweigh the risks of addiction, abuse, and misuse, the Food and Drug Administration (FDA) has required a Risk Evaluation and Mitigation Strategy (REMS) for these products. (5.2)
- Serious, life-threatening, or fatal respiratory depression may occur. Monitor closely, especially upon initiation or following a dose increase. Instruct patients to swallow OXYCONTIN tablets whole to avoid exposure to a potentially fatal dose of oxycodone. (5.3)
- Accidental ingestion of OXYCONTIN, especially by children, can result in a fatal overdose of oxycodone. (5.3)
- Prolonged use of OXYCONTIN during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated. If prolonged opioid use is required in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available. (5.4)
- Concomitant use with CYP3A4 inhibitors (or discontinuation of CYP3A4 inducers) can result in a fatal overdose of oxycodone. (5.5, 7, 12.3)
- Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death. Reserve concomitant prescribing for use in patients for whom alternative treatment options are inadequate; limit dosages and durations to the minimum required; and follow patients for signs and symptoms of respiratory depression and sedation. (5.6, 7)

Drug Abuse and Dependence

OXYCONTIN contains oxycodone, a substance with a high potential for abuse similar to other opioids including fentanyl, hydrocodone, hydromorphone, methadone, morphine, oxymorphone, and tapentadol. OXYCONTIN can be abused and is subject to misuse, addiction, and criminal diversion [see Warnings and Precautions (5.1)].

The high drug content in extended-release formulations adds to the risk of adverse outcomes from abuse and misuse.

All patients treated with opioids require careful monitoring for signs of abuse and addiction, because use of opioid analgesic products carries the risk of addiction even under appropriate medical use.

Prescription drug abuse is the intentional non-therapeutic use of a prescription drug, even once, for its rewarding psychological or physiological effects. Drug addiction is a cluster of behavioral, cognitive, and physiological phenomena that develop after repeated substance use and includes: a strong desire to take the drug, difficulties in controlling its use, persisting in its use despite harmful consequences, a higher priority given to drug use than to other activities and obligations, increased tolerance, and sometimes a physical withdrawal.

"Drug-seeking" behavior is very common in persons with substance use disorders. Drug-seeking tactics include emergency calls or visits near the end of office hours, refusal to undergo appropriate examination, testing or referral, repeated "loss" of prescriptions, tampering with prescriptions, and reluctance to provide prior medical records or contact information for other treating healthcare provider(s). "Doctor shopping" (visiting multiple prescribers to obtain additional prescriptions) is common among drug abusers and people suffering from untreated addiction. Preoccupation with achieving adequate pain relief can be appropriate behavior in a patient with poor pain control.

Abuse and addiction are separate and distinct from physical dependence and tolerance. Healthcare providers should be aware that addiction may not be accompanied by concurrent tolerance and symptoms of physical dependence in all addicts. In addition, abuse of opioids can occur in the absence of true addiction.

OXYCONTIN, like other opioids, can be diverted for non-medical use into illicit channels of distribution. Careful record-keeping of prescribing information, including quantity, frequency, and renewal requests, as required by state and federal law, is strongly advised.

Proper assessment of the patient, proper prescribing practices, periodic reevaluation of therapy, and proper dispensing and storage are appropriate measures that help to limit abuse of opioid drugs.

Risks Specific to Abuse of OXYCONTIN

OXYCONTIN is for oral use only. Abuse of OXYCONTIN poses a risk of overdose and death. The risk is increased with concurrent use of OXYCONTIN with alcohol and other central

nervous system depressants. Taking cut, broken, chewed, crushed, or dissolved OXYCONTIN enhances drug release and increases the risk of overdose and death.

With parenteral abuse, the inactive ingredients in OXYCONTIN can be expected to result in local tissue necrosis, infection, pulmonary granulomas, increased risk of endocarditis, valvular heart injury, embolism, and death. Cases of thrombotic microangiopathy (a condition characterized clinically by thrombocytopenia and microangiopathic hemolytic anemia) associated with parenteral abuse have been reported.

Parenteral drug abuse is commonly associated with transmission of infectious diseases, such as hepatitis and HIV.

Abuse Deterrence Studies

OXYCONTIN is formulated with inactive ingredients intended to make the tablet more difficult to manipulate for misuse and abuse. For the purposes of describing the results of studies of the abuse-deterrent characteristics of OXYCONTIN resulting from a change in formulation, in this section, the original formulation of OXYCONTIN, which is no longer marketed, will be referred to as “original OxyContin” and the reformulated, currently marketed product will be referred to as “OXYCONTIN.”

In Vitro Testing

In vitro physical and chemical tablet manipulation studies were performed to evaluate the success of different extraction methods in defeating the extended-release formulation. Results support that, relative to original OxyContin, there is an increase in the ability of OXYCONTIN to resist crushing, breaking, and dissolution using a variety of tools and solvents. The results of these studies also support this finding for OXYCONTIN relative to an immediate-release oxycodone. When subjected to an aqueous environment, OXYCONTIN gradually forms a viscous hydrogel (i.e., a gelatinous mass) that resists passage through a needle.

Clinical Studies

In a randomized, double-blind, placebo-controlled 5-period crossover pharmacodynamic study, 30 recreational opioid users with a history of intranasal drug abuse received intranasally administered active and placebo drug treatments. The five treatment arms were finely crushed OXYCONTIN 30 mg tablets, coarsely crushed OXYCONTIN 30 mg tablets, finely crushed original OxyContin 30 mg tablets, powdered oxycodone HCl 30 mg, and placebo. Data for finely crushed OXYCONTIN, finely crushed original OxyContin, and powdered oxycodone HCl are described below.

Drug liking was measured on a bipolar drug liking scale of 0 to 100 where 50 represents a neutral response of neither liking nor disliking, 0 represents maximum disliking and 100 represents maximum liking. Response to whether the subject would take the study drug again was also measured on a bipolar scale of 0 to 100 where 50 represents a neutral response, 0 represents the strongest negative response (“definitely would not take drug again”) and 100 represents the strongest positive response (“definitely would take drug again”).

Twenty-seven of the subjects completed the study. Incomplete dosing due to granules falling from the subjects' nostrils occurred in 34% (n=10) of subjects with finely crushed OXYCONTIN, compared with 7% (n=2) of subjects with finely crushed original OxyContin and no subjects with powdered oxycodone HCl.

The intranasal administration of finely crushed OXYCONTIN was associated with a numerically lower mean and median drug liking score and a lower mean and median score for take drug again, compared to finely crushed original OxyContin or powdered oxycodone HCl as summarized in Table 5.

Figure 1 demonstrates a comparison of drug liking for finely crushed OXYCONTIN compared to powdered oxycodone HCl in subjects who received both treatments. The Y-axis represents the percent of subjects attaining a percent reduction in drug liking for OXYCONTIN vs. oxycodone HCl powder greater than or equal to the value on the X-axis. Approximately 44% (n=12) had no reduction in liking with OXYCONTIN relative to oxycodone HCl. Approximately 56% (n=15) of subjects had some reduction in drug liking with OXYCONTIN relative to oxycodone HCl. Thirty-three percent (n=9) of subjects had a reduction of at least 30% in drug liking with OXYCONTIN compared to oxycodone HCl, and approximately 22% (n=6) of subjects had a reduction of at least 50% in drug liking with OXYCONTIN compared to oxycodone HCl.

The results of a similar analysis of drug liking for finely crushed OXYCONTIN relative to finely crushed original OxyContin were comparable to the results of finely crushed OXYCONTIN relative to powdered oxycodone HCl. Approximately 43% (n=12) of subjects had no reduction in liking with OXYCONTIN relative to original OxyContin. Approximately 57% (n=16) of subjects had some reduction in drug liking, 36% (n=10) of subjects had a reduction of at least 30% in drug liking, and approximately 29% (n=8) of subjects had a reduction of at least 50% in drug liking with OXYCONTIN compared to original OxyContin.

Summary

The in vitro data demonstrate that OXYCONTIN has physicochemical properties expected to make abuse via injection difficult. The data from the clinical study, along with support from the in vitro data, also indicate that OXYCONTIN has physicochemical properties that are expected to reduce abuse via the intranasal route. However, abuse of OXYCONTIN by these routes, as well as by the oral route, is still possible.

Additional data, including epidemiological data, when available, may provide further information on the impact of the current formulation of OXYCONTIN on the abuse liability of the drug. Accordingly, this section may be updated in the future as appropriate.

OXYCONTIN contains oxycodone, an opioid agonist and Schedule II controlled substance with an abuse liability similar to other opioid agonists, legal or illicit, including fentanyl, hydromorphone, methadone, morphine, and oxymorphone. OXYCONTIN can be abused and is subject to misuse, addiction, and criminal diversion [see Warnings and Precautions (5.1) and Drug Abuse and Dependence (9.1)].

11.2. Guidance for Industry: Abuse-Deterrent Opioids—Evaluation and Labeling

Abuse-Deterrent Opioids — Evaluation and Labeling

Guidance for Industry

**U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)**

**Clinical Medical
April 2015**

Abuse-Deterrent Opioids — Evaluation and Labeling

Guidance for Industry

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Abuse-Deterrent Opioids — Evaluation and Labeling Guidance for Industry¹

This guidance represents the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not create any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

I. INTRODUCTION

This guidance explains FDA's current thinking about the studies that should be conducted to demonstrate that a given formulation has abuse-deterrent properties. The guidance makes recommendations about how those studies should be performed and evaluated and discusses how to describe those studies and their implications in product labeling.

This guidance is intended to assist sponsors who wish to develop opioid drug products with potentially abuse-deterrent properties and is not intended to apply to products that are not opioids or opioid products that do not have the potential for abuse.

This guidance also does not address issues associated with the development or testing of generic formulations of abuse-deterrent opioid products. FDA intends to address that topic in one or more future guidance documents.

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

Prescription opioid products are an important component of modern pain management. However, abuse and misuse of these products have created a serious and growing public health problem. One potentially important step towards the goal of creating safer opioid analgesics has

¹ This guidance has been prepared by the Division of Anesthesia, Analgesia, and Addiction Products, the Office of Regulatory Policy, the Office of Surveillance and Epidemiology, the Office of Biostatistics, and the Controlled Substance Staff in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration.

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been the development of opioids that are formulated to deter abuse. FDA considers the development of these products a high public health priority.

Because opioid products are often manipulated for purposes of abuse by different routes of administration or to defeat extended-release (ER) properties, most abuse-deterrent technologies developed to date are intended to make manipulation more difficult or to make abuse of the manipulated product less attractive or less rewarding. It should be noted that these technologies have not yet proven successful at deterring the most common form of abuse—swallowing a number of intact capsules or tablets to achieve a feeling of euphoria. Moreover, the fact that a product has abuse-deterrent properties does not mean that there is no risk of abuse. It means, rather, that the risk of abuse is lower than it would be without such properties. Because opioid products must in the end be able to deliver the opioid to the patient, there may always be some abuse of these products.

For purposes of this guidance, *abuse-deterrent properties* are defined as those properties shown to meaningfully ***deter*** abuse, even if they do not fully ***prevent*** abuse. The term *abuse* is defined as the intentional, non-therapeutic use of a drug product or substance, even once, to achieve a desirable psychological or physiological effect.² Abuse is not the same as *misuse*, which refers to the intentional therapeutic use of a drug product in an inappropriate way and specifically excludes the definition of abuse.³ This guidance uses the term *abuse-deterrent* rather than *tamper-resistant* because the latter term refers to, or is used in connection with, packaging requirements applicable to certain classes of drugs, devices, and cosmetics.⁴

The science of abuse deterrence is relatively new, and both the formulation technologies and the analytical, clinical, and statistical methods for evaluating those technologies are rapidly evolving. Based on the evolving nature of the field, FDA intends to take a flexible, adaptive approach to the evaluation and labeling of potentially abuse-deterrent products. Methods for evaluating the abuse-deterrent properties of new molecular entities may have to be adapted based on the characteristics of those products and the anticipated routes of abuse. The development of an abuse-deterrent opioid product should be guided by the need to reduce the abuse known or expected to occur with similar products.

Because FDA expects that the market will foster iterative improvements in products with abuse-deterrent properties, no absolute magnitude of effect can be set for establishing abuse-deterrent characteristics. As a result, FDA intends to consider the *totality of the evidence* when reviewing the results of studies evaluating the abuse-deterrent properties of a product.

² Smith S M, Dart R C, Katz N P, et al. 2013. Classification and definition of misuse, abuse, and related events in clinical trials: ACTTION systematic review and recommendations. *Pain*, 154:2287-2296.

³ Ibid.

⁴ FDA's current Good Manufacturing Practice regulations include tamper-evident packaging requirements. See 21 CFR 211.132. There are also requirements for child resistant "special packaging" under the Poison Prevention Packaging Act and regulations adopted by the Consumer Protect Safety Commissioner (CPSC) in 16 CFR 1700.

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As with all NDA products, FDA intends to consider opioids with abuse-deterrent properties within the context of available therapy. The standard against which each product's abuse-deterrent properties are evaluated will depend on the range of abuse-deterrent and non-abuse-deterrent products on the market at the time of that application.⁵

Abuse-deterrent properties can generally be established only through comparison to another product.

FDA encourages additional scientific and clinical research that will advance the development and assessment of abuse-deterrent technologies.

FDA believes it is critical to address the problem of opioid abuse while seeking to ensure that patients in pain have appropriate access to opioid products. Moreover, it is important that opioids without abuse-deterrent properties remain available for use in some clinical settings. For example, patients in hospice care and with difficulty swallowing may need access to opioid products that are in solution or that can be crushed.

The following section describes the categories of abuse-deterrent products. The premarket and postmarket studies that should be performed to assess the impact of a potentially abuse-deterrent product are discussed in subsequent sections. Finally, information is provided about labeling for abuse-deterrent products.

III. ABUSE-DETERRENT PRODUCTS

Opioid products can be abused in a number of ways. For example, they can be swallowed whole, crushed and swallowed, crushed and snorted, crushed and smoked, or crushed, dissolved and injected. Abuse-deterrent technologies should target known or expected routes of abuse relevant to the proposed product. As a general framework, abuse-deterrent formulations can currently be categorized as follows:

1. *Physical/chemical barriers* – Physical barriers can prevent chewing, crushing, cutting, grating, or grinding of the dosage form. Chemical barriers, such as gelling agents, can resist extraction of the opioid using common solvents like water, simulated biological media, alcohol, or other organic solvents. Physical and chemical barriers can limit drug release following mechanical manipulation, or change the physical form of a drug, rendering it less amenable to abuse.
2. *Agonist/antagonist combinations* – An opioid antagonist can be added to interfere with, reduce, or defeat the euphoria associated with abuse. The antagonist can be sequestered and released only upon manipulation of the product. For example, a drug product can be

⁵ For guidance on the evaluation of abuse potential for purposes of the Controlled Substances Act (CSA), we refer sponsors to FDA's draft guidance for industry *Assessment of Abuse Potential of Drugs*. This guidance is available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM198650.pdf>. FDA guidances are available at <http://www.fda.gov/RegulatoryInformation/Guidances/default.htm>.

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formulated such that the substance that acts as an antagonist is not clinically active when the product is swallowed, but becomes active if the product is crushed and injected or snorted.

3. *Aversion* – Substances can be added to the product to produce an unpleasant effect if the dosage form is manipulated or is used at a higher dosage than directed. For example, the formulation can include a substance irritating to the nasal mucosa if ground and snorted.
4. *Delivery System* (including use of depot injectable formulations and implants) – Certain drug release designs or the method of drug delivery can offer resistance to abuse. For example, sustained-release depot injectable formulation or a subcutaneous implant may be difficult to manipulate.
5. *New molecular entities and prodrugs* – The properties of a new molecular entity (NME) or prodrug could include the need for enzymatic activation, different receptor binding profiles, slower penetration into the central nervous system, or other novel effects. Prodrugs with abuse-deterrent properties could provide a chemical barrier to the in vitro conversion to the parent opioid, which may deter the abuse of the parent opioid. New molecular entities and prodrugs are subject to evaluation of abuse potential for purposes of the Controlled Substances Act (CSA).
6. *Combination* – Two or more of the above methods could be combined to deter abuse.
7. *Novel approaches* – This category encompasses novel approaches or technologies that are not captured in the previous categories.

IV. PREMARKET STUDIES

First and foremost, any studies designed to evaluate the abuse-deterrent characteristics of an opioid formulation should be scientifically rigorous. Important general considerations for the design of these studies include the appropriateness of positive controls⁶ and comparator drugs, outcome measures, data analyses to permit a meaningful statistical analysis, and selection of subjects for the study.

The evaluation of an abuse-deterrent formulation should take into consideration the known routes of abuse for the non-abuse-deterrent predecessor or similar products, as well as anticipate the effect that deterring abuse by one route may have on shifting abuse to other, possibly riskier route. For example, if a product is known to be abused using nasal and intravenous routes, developing deterrent properties for the nasal route in the absence of deterrent properties for the intravenous route risks shifting abusers from the nasal to the intravenous route, which is associated with a greater risk for the spread of infectious diseases.

Another concept that should be considered is whether the deterrent effects can be expected to have a meaningful impact on the overall abuse of the product. For example, immediate-release (IR) opioid and acetaminophen combination products are predominantly abused using the oral

⁶ For purposes of this guidance, a positive control is an opioid drug product or drug substance expected to result in a predictable opioid drug liking effect and has a known potential for, or history of, abuse.

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route. Demonstrating a deterrent effect by the nasal route may not meaningfully reduce overall abuse of the product.

FDA is committed to retaining a flexible, adaptive approach to evaluating potentially abuse-deterrent opioid drug products. This flexibility is intended to permit a sponsor to tailor the development program to suit the abuse-deterrent characteristics of their product and the routes of abuse for that product. The adaptive aspect is intended to permit a sponsor to take into consideration the relevant products on the market at the time they are developing their product, so that appropriate non-abuse-deterrent and abuse-deterrent comparators can be used. For example, for some proposed products the appropriate comparator may be a conventional formulation. However, if there are similar approved products with abuse-deterrent properties described in labeling, the appropriate comparator should be one of those abuse-deterrent products.

The following sections describe three categories of premarket studies. Although, in general, any development program for studying abuse-deterrent technologies should include data from all three categories of studies, there may be exceptions. For example, a formulation with a sequestered antagonist may intentionally be formulated not to resist crushing, so testing the syringeability of the product may not be relevant. In most cases, however, to obtain a full and scientifically rigorous understanding of the impact of a technology or technologies on a product's abuse potential, data from each of the following three categories of premarket studies are appropriate:

1. Laboratory-based in vitro manipulation and extraction studies (Category 1)
2. Pharmacokinetic studies (Category 2)
3. Clinical abuse potential studies (Category 3)

The results of Category 1 studies may influence the design of Category 2 pharmacokinetic studies and Category 3 clinical abuse potential studies by suggesting the methods of manipulation that would yield the greatest release of opioid. The results of Category 2 studies may influence the need for Category 3 studies of clinical abuse potential and the designs and goals of these studies. For example, if the extended-release characteristics of an abuse-deterrent opioid formulation cannot be defeated and the pharmacokinetic profile remains unchanged following oral or nasal administration of the manipulated product, oral and nasal studies of abuse potential may not be necessary.

Additional studies (i.e., Category 4 studies) analyze postmarket data to assess the impact of an abuse-deterrent formulation on actual abuse. Nonclinical drug discrimination studies are useful in the evaluation of the abuse potential of a drug, but their utility in predicting the impact of abuse-deterrent properties on human behavior has not been established.⁷

⁷ See FDA draft guidance for industry, *Assessment of Abuse Potential of Drugs* see <http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm198650.pdf>.

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A. Laboratory Manipulation and Extraction Studies (Category 1)

The goal of laboratory-based Category 1 studies should be to evaluate the ease with which the potentially abuse-deterrent properties of a formulation can be defeated or compromised. This information should be used when designing Category 2 and Category 3 studies. These studies are critical to the understanding of product characteristics and performance.⁸

Methodologically, these studies should be designed with knowledge of the physicochemical properties of the product and the methods available to abusers to manipulate the product and should be conducted on the to-be-marketed formulation. Sponsors should consider both the mechanisms by which abusers can be expected to attempt to deliberately overcome the abuse-deterrent properties of the product as well as the ways that patients may alter the formulation (unintentionally or intentionally) that change the rate or amount of drug released (e.g., dose dumping may occur when taking the product with alcohol or when the product is cut, chewed, or crushed). Testing should provide information sufficient to fully characterize the product's abuse-deterrent properties, including the degree of effort required to bypass or defeat those properties. In some cases, when designing in vitro studies, it may be useful to obtain information from prescription opioid abusers about how they would manipulate and abuse an abuse-deterrent product.

In vitro studies should assess various simple and sophisticated mechanical and chemical ways a drug could be manipulated, such as by (1) defeating or compromising the controlled release of an opioid from ER formulations for purposes of abuse by different routes of administration; (2) preparing an IR formulation for alternative routes of administration; or (3) separating the opioid antagonist, if present, from the opioid agonist, thus compromising the product's abuse-deterrent properties. The goal of these studies is to manipulate the product to the point of defeating its abuse-deterrent properties. Once this goal is achieved, it is no longer necessary to continue experiments using more sophisticated methods. For example, if 90% of the opioid can be extracted under a set of conditions in 10 minutes, there is no need to test the same condition for 30 minutes.

The test product should be compared to appropriate comparator products for ease of mechanical manipulation. The ability to crush, cut, grate, or grind the product formulation using readily available items such as spoons, cutters, and coffee grinders should be assessed. Particular attention should be given to particle size distribution following each mode of physical manipulation because particle size may influence the rate of opioid extraction from manipulated product. The effect of heat and cold on mechanical manipulation should also be studied.

Extractability and solubility studies should be designed to determine whether any of the formulation components might be differentially solubilized and extracted, allowing an abuser to

⁸ This topic has been discussed at meetings of the Anesthetic & Life Support Drugs Advisory Committee and the Drug Safety & Risk Management Advisory Committee (*NDA 022272, OxyContin*, May 5, 2008, and September 24, 2009). Additional information on these meetings is available on FDA's web site at the following location: <http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AnestheticAndAnalgesicDrugProductsAdvisoryCommittee/UCM187082.pdf>.

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bypass the drug's abuse-deterrent properties. In addition to extraction and solubility studies, an assessment should be made to determine if free-base opioid can be precipitated from solution by pH adjustment. After establishing how a product could be manipulated, chemical extraction of the opioid from the intact and the manipulated product should be assessed and compared to opioid extraction from the selected intact and similarly manipulated comparator products.

The ease of extracting the opioid from the intact and manipulated product should be determined using a variety of solvents that are commonly available (e.g., water, vinegar, ethanol, isopropanol, acetone, mineral spirits) and those that have potentially relevant solvent characteristics (e.g., pH, polarity, protic vs. aprotic). The effects of time, temperature, pH, and agitation on solvent extraction should also be determined. For products containing more than one drug substance, extractability and solubility studies should be designed to determine whether any of the active ingredients might be differentially solubilized and extracted. Sampling times should start early (e.g., 30 seconds) and continue until at least 80% of the opioid has been released, or 12 hours has been reached. The in vitro drug-release characteristics of the intact and manipulated product should also be compared using a discriminatory and robust dissolution method.

In addition to the general evaluation of the effects of physical and chemical manipulation on the product, there are important route-specific data that should be generated, as follows:

- For a product with potential for abuse by the nasal route, the particle size distribution following attempted manipulation by various methods should be established, and the method that provides the smallest particle size should be used in subsequent studies.
- For a product with potential for abuse by smoking, the amount of drug produced by vaporization at temperatures encompassing the range from the melting point of the active ingredient to its degradation point should be determined. Appropriate controls, such as pure active ingredient, both in salt and free-base form should be included in these assessments.
- For a product with potential for abuse by injection, the amount of opioid that can be obtained in a syringe should be based on studies of intact and manipulated test product and comparator(s) using small volumes of water (5-10 mL) at room temperature and at 90° C – 95° C with and without agitation. Extraction times should range from 30 seconds to 30 minutes. The amount of opioid extracted, the volume of solution collected and the viscosity of the samples should be recorded. The ability to get the sample into a syringe and expel the sample using needles of various gauges should also be explored.

The following examples illustrate the kinds of outcomes that in vitro studies should evaluate.

1. Characteristics of the product by crushing, grinding or melting, or by changing the intact formulation using other methods that would limit nasal administration of the manipulated product, and/or that would limit dissolution of the manipulated product and incorporation into a solvent that could then be injected by intravenous or subcutaneous routes.

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2. Quantity of the opioid extracted from the product following the various methods attempted that could be used for injection by intravenous or subcutaneous routes and a description of any barriers resulting from attempts at dissolution for drawing the drug into a syringe.
3. Quantity of opioid antagonist released from an agonist/antagonist combination when it is manipulated for administration by ingestion, nasal administration, or injection.
4. Quantity of opioid product following in vitro manipulation of the prodrug.

B. Pharmacokinetic Studies (Category 2)

The goal of the clinical pharmacokinetic studies, Category 2, should be to understand the in vivo properties of the formulation by comparing the pharmacokinetic profiles of the manipulated formulation with the intact formulation and with manipulated and intact formulations of the comparator drugs through one or more routes of administration. Even though the same routes of administration should be studied for the new product and comparators, if specific circumstances prevent this approach, the study design should be discussed with FDA. The method of manipulation used for the pharmacokinetic studies should be based on the methods explored during in vitro testing that can be expected to result in the greatest drug release. The routes of administration chosen should be relevant to the proposed product, and likely will be based on what is known about the abuse of similar products. Note that, for some development programs, it may be preferable to combine measures of pharmacokinetic parameters for Category 3 studies, in which case separate Category 2 studies may not be necessary.

In general, the pharmacokinetic profile for the oral route of administration should be studied. Appropriate study subjects for Category 2 studies include healthy volunteers as long as naltrexone is used to block the pharmacodynamic effects of the opioids.

Depending on the product, it may be important to evaluate the pharmacokinetic profile for the nasal route of administration as well. For nasal pharmacokinetic studies, it is important to weigh the risk to the subject based on the excipients in the formulation. Only subjects with a history of nasal abuse of opioids should be recruited for these studies. As with the oral route of administration, it may be possible to combine the pharmacokinetic assessment and the pharmacodynamic assessment in one clinical abuse potential study with sampling for the pharmacokinetic analysis.

Relevant pharmacokinetic parameters for the opioid drug and any psychoactive metabolites that should be measured in these studies include the following.

- Maximum concentration (C_{max})
- Time to maximum concentration (T_{max})
- Area under the curve (AUC_{0-t} and $AUC_{0-\infty}$)
- Relevant partial AUC, including early time points such as AUC_{0-30} minutes or AUC_{0-2} hours, the period of time when C_{max} is expected
- Terminal elimination half-life ($T_{1/2}$)

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Traditional pharmacokinetic study designs should be employed (e.g., crossover designs), and the results should be analyzed using bioequivalence methods. The rate of rise of drug concentration should be assessed when possible because it is thought to contribute to differential abuse potential among drugs, formulations, and routes of administration.⁹ To support these analyses, it is important to have specimen collection and analysis time points sufficient to cover the onset, peak, and offset of the effects of both IR and ER formulations, in both the intact and manipulated conditions. In addition, these data are necessary to calculate the relevant partial area under the curve, which should capture the time to maximum concentration of the opioid.

If food and alcohol alter the pharmacokinetic parameters of the formulation, data should be provided to characterize those effects.¹⁰ If food significantly increases systemic exposure of the intact formulation, the underlying mechanism for the food effect should be established by assessing whether the effect is based on the drug substance or the formulation and whether the effect is present with intact product as well as with manipulated product. When food is expected to increase exposure, subsequent abuse potential studies of the oral route should be conducted in the fed state to maximize the potential systemic exposure.

In addition to the pharmacokinetic profile of the opioid, for agonist/antagonist combinations , the pharmacokinetic characteristics of the antagonist should be defined for the intact product as well as for the manipulated formulation.

As with all clinical studies, adverse events should be collected, and those that can provide additional insight about the abuse-deterrent effects are especially important. For example, if the manipulated formulation is abused by snorting, it would be important to assess adverse events related to intranasal tolerability.

C. Clinical Abuse Potential Studies (Category 3)

In addition to their use by FDA to formulate its scheduling recommendation under the CSA for drug products containing a controlled substance, clinical studies of abuse potential, Category 3, are important for assessing the impact of potentially abuse-deterrent properties. As discussed in

⁹ References suggesting that drugs associated with a rapid onset of action are associated with greater abuse potential include:

Abreu M E, Bigelow G E, Fleisher L, and Walsh S L. 2001. Effect of intravenous injection speed on responses to cocaine and hydromorphone in humans. *Psychopharmacology*, 154:76-84.

de Wit H, Bodker B, and Ambre J. 1992. Rate of increase of plasma drug level influences subjective responses in humans. *Psychopharmacology*, 107:352-358.

de Wit H, Didish S, and Ambre J. 1993. Subjective and behavioral effects of diazepam depend on its rate of onset. *Psychopharmacology*, 112: 324-330.

¹⁰ FDA has issued a draft guidance on this topic (*Assessment of Abuse Potential of Drugs*). Once finalized, it will represent FDA's current thinking on this topic.

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FDA's guidance on that topic,¹¹ the preferred design is a randomized, double-blind, placebo-controlled and positive controlled crossover study. These studies generally are conducted in a drug-experienced, recreational user population. The use of a pre-qualification phase (see section 2 below) to identify subjects who can reproducibly distinguish active drug from placebo is a common enrichment strategy used to improve the power of the study to establish a difference between treatments.

Additional considerations applicable to clinical abuse potential studies used to assess potentially abuse-deterrent properties are discussed below. For products that are not susceptible to manipulation based on Category 1 and 2 testing, study designs for Category 3 testing should be discussed with FDA.

1. Blinding

Clinical studies of abuse potential should use a randomized, double-blind, placebo-controlled and positive controlled crossover design. Because study subjects are recreational drug users and familiar with the effects of the drug substances being studied, the double-dummy technique or other techniques should be used to ensure the blinding of all tests when possible. However, alternative designs may be suitable when the blinding of the study drug and the positive control cannot be maintained and treatment by period interactions may lead to sequence effects in a crossover design. For example, a parallel design may be useful when studying the intranasal route of administration, where subjects may be able to see the differences in volume or color between test drug and placebo or positive control, or when it is not possible to create similar results from manipulation, such as particle size from crushing. In these circumstances, early discussion with FDA is recommended.

For clinical abuse potential studies in which the subjects will snort test samples, administration of the samples in a narrow neck, opaque container with a pre-inserted straw may help facilitate blinding. However, even though subjects might not be able to see the sample, un-blinding may still occur due to the physical properties of samples with similar particle size distribution. In some formulations, higher crushed tablet/capsule volume or larger particle size may inhibit complete intranasal administration thereby contributing to the deterrence effects. To be able to evaluate these effects, it may be necessary to maintain differences in tablet/capsule volume between the potentially abuse-deterrent formulation and the comparator. To facilitate blinding and maintain the crossover design, placebos matched to each of the differing weights or particle sizes may be useful. The details of the preparation of the samples should be provided in the study protocol.

2. Pre-qualification Phase

The purpose of the pre-qualification phase is to increase the power of a study to detect differences in the abuse potential of the various formulations of drug and placebo.¹² In general,

¹¹ Ibid.

¹² An additional advantage of a pre-qualification phase is that it helps familiarize subjects with and train them in the use of various scales and questionnaires that measure subjective effects.

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the pre-qualification phase should ensure that subjects can distinguish between placebo and a conventional IR formulation of the same opioid being developed in an abuse-deterrent formulation, using the same route of administration as planned for the assessment phase. There is little value in having subjects unable to distinguish placebo from active drug continue in the study. The positive control should include a strength that is at least equal to the lowest strength selected for the assessment during the clinical phase. An important aspect of the pre-qualification phase is assessing the ability of subjects to tolerate the study dose. If the dose used in the pre-qualification phase is lower than the lowest strength planned for the assessment phase, some subjects may not be able to tolerate the higher dose that will be administered in the assessment phase. Thus, when tolerability may be an issue, particularly if more than one dose is planned for the assessment phase, a pre-qualification dose that is no lower than the lowest dose planned may be the most efficient choice to establish that the subject can distinguish active drug from placebo and can tolerate the study drug in the range to be tested. For example, a 30 mg or 45 mg dose of opioid could be used in the pre-qualification phase when a 30 mg and 60 mg doses will be assessed in the clinical phase.

Qualifying criteria that help identify subjects with an acceptable placebo response and an acceptable response for the positive control should be pre-specified in the study protocol. After a range for an acceptable placebo response is set, a minimum value for the maximum effect (E_{max}) for the positive control should be defined. The minimum E_{max} for the positive control may vary from measure to measure, and from study to study. However, an acceptable response for the positive control should not overlap with the acceptable range for placebo response.

3. Assessment Phase

The potentially abuse-deterrent product should be compared to a positive control, and the positive control should be compared to placebo to validate the study. For an IR product with potentially abuse-deterrent properties, the positive control should be an IR formulation of the same opioid. For an ER formulation with potentially abuse-deterrent properties, the positive control could be an IR formulation of the same opioid or an ER formulation of the same opioid. In general, these studies should include one strength of the positive control which is associated with high levels of drug liking. However, when assessing drug liking through the intranasal route, the use of two strengths of the positive control may be helpful to both identify a strength of the positive control associated with high drug liking scores and to validate the study.

If there are no approved products with the same drug substance, the positive control should be a drug that, based on pharmacological profile or nonclinical data, can be expected to have similar pharmacodynamic effects. Selection of the positive control in this setting should be discussed with FDA.

4. Subjects

Studies should be conducted in opioid-experienced, recreational drug users who have experience with the particular route of abuse being studied. Subjects should generally not be physically dependent and should not be currently seeking or participating in treatment for drug abuse such that participating in the study could make them vulnerable to relapse. Depending on the

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formulation being studied, however, clinical abuse potential studies can be conducted in physically dependent subjects. For example, if the deterrent product contains an opioid antagonist, clinical abuse potential studies in a physically dependent population may provide information not only on the drug liking of the product, but on the ability of the antagonist to precipitate withdrawal in this population.

Detailed characteristics of the study population with respect to past and current drug use and abuse should be captured (e.g., drugs abused, drug of choice, duration of abuse or abstinence).

5. Route of Administration, Dose Selection, Manipulation Mode, and Sample Preparation

The selection of the route(s) of administration should be based on epidemiological data showing that a selected route is a relevant route of abuse. For NMEs, the sponsor should review the relevant routes of abuse for products similar to the test product and discuss the selected routes with FDA. For each relevant route of administration, the potentially abuse-deterrent product and comparator should be manipulated based on the results of Category 1 studies to cause the highest release of the opioid and the highest plasma levels. The dose of the opioid selected for the study should be known to produce high levels of liking in non-tolerant opioid-experienced recreational users.

For studies using the intranasal route of administration, the preparation of the samples is extremely important. The potentially abuse-deterrent product and comparator study drug should be produced with similar particle size distribution based on a detailed protocol for the preparation of the samples, even if different methods are necessary to do so.¹³ With some formulations, a high volume of the crushed tablet/capsule or larger particle size may inhibit complete intranasal administration and, thereby, contribute to deterrence effects. To evaluate these effects, it may be necessary to maintain differences in tablet/capsule volume between the potentially abuse-deterrent product and the comparator.

For studies using the intravenous route of administration, the oral formulations may not be safe for intravenous use depending on the excipients used in the formulation. In place of the manipulated oral formulation, a solution for injection should be prepared using approved, commercially available parenteral products when available, or products suitably formulated for the study. The amount of the opioid and that of the antagonist, when relevant, should be based on extrapolation from in vitro extraction studies of manipulated solid formulations.

6. Outcome Measures and Data Interpretation

In abuse potential studies, the primary method for evaluating the subjective effects of drugs should be through the use of standardized instruments.

¹³ Available safety-related information on the use of the various excipients through the intranasal route should be provided. Additionally, some sponsors have conducted intranasal tolerability studies before the abuse potential studies to evaluate irritation of the nasal cavity, nasal congestion, and discharge, among other measures.

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In typical abuse potential studies, several instruments have been used to measure subjective responses predictive of the likelihood of abuse. These instruments include:

- Visual Analogue Scales (VAS) – used for drug liking, good effects, bad effects, and other drug abuse-related effects
- Profile of Mood States

The VAS should be the primary measure for drug liking because it appears to correlate most directly with potential for abuse. Other measures of particular interest include assessment of likelihood to take the drug again and assessment of overall drug liking.¹⁴

These measures can be assessed using either a unipolar or bipolar scale, and a rationale should be provided for the choice for a particular scale. In general, FDA recommends using a bipolar scale for the primary measure of drug liking. Unipolar scales have been used to measure other drug effects, such as good and bad effects. Regardless of whether a unipolar or bipolar scale is selected, FDA recommends that for purposes of training subjects, the same scale be used in the pre-qualification and assessment phases.

7. Data Interpretation

For clinical studies of abuse potential conducted on potentially abuse-deterrent opioid drug products, the primary analysis should be the difference in means of the E_{max}¹⁵ for the primary measure(s) based on the population of study completers. A statistical analysis plan (SAP) should be included in the study protocol or submitted as a separate document before un-blinding the study. The sponsor should provide data and dropout information for non-completers. To ensure adequate power, the sponsor should take into account that there will be subjects who drop out of the study early and plan the sample size calculation accordingly. Proper planning should avoid any need to replace subjects who discontinue without completing the study.

Additional pharmacodynamic measures, including positive subjective effects other than drug liking (e.g., take drug again, high, overall drug liking) and other subject-rated assessments, are generally considered secondary endpoints. Other subject-rated assessments of interest include: alertness; drowsiness; nausea; and, when the intranasal route is used, intranasal irritation, burning, need to blow nose, runny nose/nasal discharge, facial pain/pressure, and nasal congestion.

Some sponsors provide descriptive statistics including mean, standard error, median, and interquartile range, calculated for all pharmacodynamic endpoints by time and treatment.¹⁶ What

¹⁴ Overall drug liking measures the user's retrospective assessment of a drug, whereas VAS for drug liking measures the user's immediate assessment.

¹⁵ In general, the primary endpoint of interest is drug liking, and the E_{max} is captured within 8 hours after dosing. However, the timeframe of measuring the maximum response will be determined by the pharmacokinetic and pharmacodynamic parameters of the formulations studied.

¹⁶ See Statistical Analysis Section for further guidance.

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constitutes a clinically significant difference in drug liking, between the manipulated and intact versions of the potentially abuse-deterrent product and positive control, is an area requiring further research and will be evaluated on a case-by-case basis. Analysis of postmarket data on abuse levels associated with the potentially abuse-deterrent product being studied may help to support the findings from abuse potential studies.

In addition, when interpreting results from clinical abuse potential studies, attention should be given to the profile of subjective effects produced by the manipulated and intact formulation in terms of onset, peak duration of activity, and offset. The rate of rise of drug onset for the intact and manipulated potentially abuse-deterrent product should be given appropriate weight in the overall analysis of the abuse-deterrent properties. A more rapid onset of action or a shorter time-to-reach peak effect is generally associated with greater abuse potential. Regarding the duration of effect, it may be difficult to interpret the abuse potential of a formulation that produces a sustained liking effect when taken intact or after manipulation, though lower than that produced by the positive control formulation.

The overall assessment of abuse potential should be based on the pattern of findings across all of the measures. In addition, qualitative aspects of the findings, such as the steepness of the drug liking response and duration of the liking effects associated with manipulated formulations, should be taken into consideration, along with other positive effects and negative effects.

8. Statistical Analysis

a. Background

The overall goal of a clinical study of abuse potential is to assess a number of abuse potential outcome measures (e.g., drug liking VAS) in the potentially abuse-deterrent product (T) relative to a formulation of the drug without abuse-deterrent properties (C), or a newly formulated opioid product (positive control). Substantial decreases in the responses for the potentially abuse-deterrent formulation compared to the positive control are evidence of deterrence.

A clinical study of abuse potential should be validated by comparing the responses to C with those of placebo (P). Thereafter, the assessment of the abuse-deterrence properties of T is of primary interest. This can be achieved by comparing the difference in means between C and T with a *margin* for abuse potential measures and comparing the difference between C and T relative to C in drug liking on a bipolar VAS.

The statistical analysis of the data in a clinical study should begin with descriptive statistics making up tabulations and graphs that include tables of the mean, standard error, and other summary statistics: minimum, Q1, median, Q3, and maximum of the responses of interest for each treatment and for each paired difference among treatments.

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Useful graphs include mean time course profiles, heat-maps,¹⁷ and continuous responder profiles.

The next subsection describes the statistical test that sponsors should use for the primary analysis of E_{max} on the VAS for drug liking. An analysis of the percent reduction in drug liking for T relative to C on the individual level in subsection c is recommended as a secondary analysis.

b. Primary analyses

The primary analysis of abuse-deterrent effects should be based on the comparison of means¹⁸ between crushed, chewed, or otherwise modified T and C with an abuse deterrence margin on drug liking VAS. That is, test

$$H_0 : \mu_C - \mu_T \leq \delta_1 \text{ versus } H_a : \mu_C - \mu_T > \delta_1$$

where $\delta_1 = \delta^*(\mu_C - 50)$, and $0 < \delta^* < 1$. Because C is an opioid drug, the validation test also needs a margin, say δ_2 . That is,

$$H_0 : \mu_C - \mu_P \leq \delta_2 \text{ versus } H_a : \mu_C - \mu_P > \delta_2$$

where $\delta_2 \geq 15$.

The significant level for both tests is 2.5%.

The actual value of δ_1 is related to μ_C , hence, it may vary according to abuse potential measures and the route of drug administration. The δ^* should be pre-specified in the protocol. We also suggest the use of 95% confidence intervals to assess both the differences $\mu_C - \mu_T$ and $\mu_C - \mu_P$.

c. Secondary analyses

In addition to the primary analysis, an analysis should be performed of the percent reduction for the potentially abuse-deterrent product T relative to C from each individual study subject for drug liking VAS on a bipolar scale from 0 to 100. One definition for percent reduction for individual subjects is as follows:

$$\% reduction = \frac{c_i - t_i}{c_i - p_i} \times 100\%, \quad i = 1, 2, \dots, n,$$

where c_i , t_i and p_i are the E_{max} values for C , T , and P from the i th subject, respectively; n is the sample size.

¹⁷ Chen L and Wang Y. 2012. Heat map displays for data from human abuse potential crossover studies. *Drug Information Journal*, 46:701:707.

¹⁸ If a nonparametric method is necessary, analysis of the median difference in E_{max} may be appropriate.

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However, this definition is problematic because for two subjects having the same E_{\max} values for T and C ($t_1 = t_2$ and $c_1 = c_2$), the larger the placebo response, the greater the percent reduction. A more appropriate definition of percent reduction can be derived by replacing p_i by the neutral score 50 on a bipolar scale; that is,

$$\% \text{ reduction} = \frac{c_i - t_i}{c_i - 50} \times 100\%, i = 1, 2, \dots, n$$

where we assume that $c_i > 50$. In case some subjects have $c_i \leq 50$, define % reduction = 0.

Note that even though most abuse potential studies have a pre-qualification phase, approximately 10% of subjects still have placebo responses p_i over 65, with 5% over 75 in the assessment phase. Consequently, it may be necessary to penalize subjects with large values of p_i in computing percent reduction. For example, the percent reduction could be multiplied by an adjustment factor that equals 1 when p_i is around 50 or less and decreases from 1 when p_i is large. Sponsors should discuss with FDA the need for an adjustment factor in computing percent reduction and an appropriate formula for defining the penalty to be applied before finalizing the study protocol.

Two approaches for assessing the deterrent effects using percent reduction for crossover design studies are provided below. Note that when a parallel design is used, the percent reduction for individual subjects is not applicable, and the primary analysis may also serve the purpose for assessing the percent reduction based on $\mu_C - \mu_T$ related to $\mu_C - 50$.

- **Responder Analysis**

A *responder* is defined as a subject who had at least $\delta^* 100\%$ of reduction, in E_{\max} for T relative to C. To ensure that a majority of subjects are responders, a proportion test can be used to test the null hypothesis that 50% or fewer subjects are responders. That is, test

$$H_0 : p^* \leq 50\% \text{ versus } H_a : p^* > 50\%$$

at the 2.5% significance level where p^* denotes the percentage of responders. The 95% confidence interval of p^* can also be calculated.

- **Analysis of the Median Percent Reduction**

The median of the percent reduction (ptr) is a descriptive measure of central tendency of ptr . At most 50% of subjects have ptr less than the median, and at most 50% of subjects have ptr greater than the median. If the median of ptr is equal to 30%, for example, it means that approximately 50% of subjects have greater than or equal to a 30% reduction.

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For assessing deterrent effects, we can test

$$H_0 : \text{median}(\text{ptr}) \leq DR\% \text{ versus } H_a : \text{median}(\text{ptr}) > DR\%$$

at the 2.5% significance level, where DR denotes deterrent reduction. To be consistent with the responder analysis, we recommend DR % = $\delta^* 100\%$. If the distribution of *ptr* is symmetric, the Wilcoxon-signed rank test can be used to test the null hypothesis that the $\text{median}(\text{ptr}) \leq DR\%$, and a 95% confidence interval for the median based on this test can be readily calculated using standard methods. Otherwise, the sign test should be used or an alternate method of this test can be pre-specified in the SAP.

Sponsors should pre-specify one of the two analysis methods for the percent reduction in their SAP in addition to the primary analysis in their clinical studies and discuss with FDA the definition of a responder in the responder analysis or the value of DR% used in the analysis of the median percent reduction before finalizing the study protocol.

d. Multiplicity

Whether or not an adjustment for multiplicity is needed for claiming significant results on the primary or key secondary endpoints varies from study to study. Sponsors should refer to the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guidance *E9 Statistical Principles for Clinical Trials*¹⁹ for statistical principles regarding the multiplicity adjustment.

V. POSTMARKET STUDIES (CATEGORY 4)

Premarket studies focus on assessing the potentially abuse-deterrent properties of a product under controlled conditions. The goal of postmarket²⁰ studies, Category 4, is to determine whether the marketing of a product with abuse-deterrent properties results in meaningful reductions in abuse, misuse, and related adverse clinical outcomes, including addiction, overdose, and death in the post-approval setting. As more abuse-deterrent products are approved, it is possible that the amount of reduction observed in an epidemiologic study may also change. Consequently, a reduction that is deemed meaningful at one time may not be meaningful at another. Given the changing landscape, a numerical threshold cannot define what would be considered a meaningful reduction.

Currently, data on the impact of an abuse-deterrent product on drug abuse in the U.S. population are limited, and thus the optimal data sources, study variables, design features, analytical

¹⁹ ICH guidelines are available on FDA's guidance webpage at <http://www.fda.gov/RegulatoryInformation/Guidances/default.htm>.

²⁰ FDA requires postmarket studies for all opioids with abuse-deterrent labeling claims. For more information on postmarket requirements, see <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Post-marketingPhaseIVCommitments/ucm070766.htm>.

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techniques, and outcomes of interest of postmarket epidemiologic studies are not fully established.

Postmarket evaluations of abuse deterrence fall into two categories—formal studies and supportive information. Sponsors should submit protocols to FDA for all formal studies of abuse deterrence. Supportive information can also be submitted to FDA, but cannot substitute for formal studies.

A wide range of interrelated behavioral, clinical, and societal factors contribute to drug abuse; therefore, the effects of an abuse-deterrent formulation can manifest in a variety of ways.

Understanding the actual impact of a particular abuse-deterrent formulation may require using a variety of study designs to examine different abuse-related outcomes in given populations of interest. Generally, multiple formal studies using a variety of data sources should be conducted to provide insights into product-specific abuse and the effect of an abuse-deterrent product on the outcomes of interest for other opioid drug products. The use of multiple study designs will also generally help with assessment of the impact of abuse-deterrent products on the full spectrum of abuse-related outcomes (i.e., addiction, overdose, and death) and to characterize and quantify the relevant clinical events that are associated with these outcomes.

Recognizing that the current thinking in this area may change, the following subsections provide recommendations for designing postmarket epidemiologic studies that are capable of detecting a change in the occurrence of abuse as a result of a drug product's abuse-deterrent properties.

A. Formal Studies

1. General Characteristics

Formal studies have the following characteristics:

1. They are hypothesis-driven, population-based, observational evaluations that follow good epidemiological practices^{21,22} and use outcomes that provide meaningful measures of abuse deterrence.
2. They capture one or more outcomes that can be used to assess meaningful reductions in misuse, abuse, addiction, overdose, and death.
3. They produce estimates of abuse and related clinical outcomes that are nationally representative, or are based on data from multiple large geographic regions that can reasonably be generalized to the national level. In the absence of nationally generalizable

²¹ See FDA guidance *Best Practices for Conducting and Reporting Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data*, available at <http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm243537.pdf>.

²² International Society for Pharmacoepidemiology and Risk Management, Guidelines for Good Practices and Pharmacoepidemiologic Studies, available at http://www.pharmacoepi.org/resources/guidelines_08027.cfm, accessed January 25, 2015.

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data, smaller or regional studies may be informative, but must be accompanied by a clear explanation of their representativeness and generalizability for appropriate interpretation.

4. They assess overall and route-specific (i.e., injected, snorted, smoked) changes in abuse levels that are associated with an abuse-deterrent product.
5. They are sufficiently powered statistically to assess meaningful changes in drug abuse and are of sufficient duration to examine trends in abuse following the marketing of the abuse-deterrent product. The necessary duration of the studies will depend on a variety of factors, including drug utilization and market share, early postmarket abuse deterrence data, and changes in the prescription opioid or illicit drug market.

2. Study Design Features

The epidemiologic methods and data sources that underlie formal postmarket studies to evaluate the effect of abuse-deterrent formulations are evolving, and best practices have not been established. In addition, characterizing the relevant clinical events that are most useful for understanding the actual impact of a product on abuse-related adverse events is also an evolving science. Based on the current state of this field, we provide below some basic guidelines on recommended study design features that will enable FDA to evaluate the results of formal studies.

1. The study hypothesis and its relationship to assessing abuse deterrence should be clearly stated. The study hypothesis should also include the route(s) of abuse that will be studied.
2. An understanding of each data source is important to the design and interpretation of the study. A description of each data source should be provided in the protocol and should include if and how the data source captures drugs, study outcomes, drug formulation, and route of abuse. The sampling methods, study population, or catchment area for the data source should be clearly described.²³
3. The choice of population(s) in each study should be carefully considered. The populations included in the study should be described in the protocol. At least one study should include a high-risk population, such as a population of known drug abusers, but formal studies should not be limited to only high-risk populations.
4. The protocol and study reports should thoroughly define the study outcomes. The choice of the outcome measure(s) should be justified. Formal studies should, as a group, capture all relevant outcomes: misuse, abuse, addiction, overdose, and death, as well as misuse and abuse clinical outcomes. Overall and route-specific misuse and abuse estimates should include prevalence and frequency of abuse. Clinical outcomes should include, when possible, an assessment of severity of abuse outcomes (e.g., addiction or overdose).

²³ See FDA guidance *Best Practices for Conducting and Reporting Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data*.

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5. Both population- and drug utilization-based estimates should be included in the study protocol.²⁴ Drug utilization-based estimates should use multiple denominators. The denominators are generally the number of prescriptions and the number of extended units (e.g., tablets or capsules). The catchment area for drug utilization data should be specified, particularly for sub-national or regional populations.
6. Sponsors should list all proposed opioid comparators and describe the rationale behind their inclusion. When branded and generic versions of a comparator are marketed, all should be included in the study when possible because many data sources used in abuse studies can identify only active ingredients and do not distinguish between branded and generic products or among multiple generic products. Information should be provided on the ability of data sources and study participants to accurately discriminate among different opioid products and formulations. The choice of comparator is critical for determining if a reduction in drug abuse is the result of a product's abuse-deterrent properties or the result of other factors (e.g., educational programs, prescription drug monitoring programs, changes in law enforcement policies, and the availability of other drugs) or secular trends. The choice of comparators will depend on the particular abuse-deterrent product studied and the opioid market environment at the time the study is initiated. Multiple comparators should be used to achieve the most complete picture of the impact of a product's abuse-deterrent properties. For the purposes of hypotheses, some comparators should be selected and justified as primary comparators in the study protocol before data collection, with additional comparators providing context. The following are examples of several potential abuse-deterrent study comparator scenarios.

If an abuse-deterrent formulation of a previously marketed product is introduced to the market, the primary comparators should include historical and currently available non-abuse-deterrent formulations of the products (including branded and generic whenever possible). Additional individual opioid products should be included as well and should be agreed upon with FDA and identified before the start of the study.

If a new abuse-deterrent product does not have an historical or currently available non-abuse-deterrent version of the same opioid, an appropriate group of comparators should be identified before the start of the study through mutual agreement with FDA. Examples of appropriate primary comparators include immediate release non-abuse-deterrent products with the same active moiety and/or a non-abuse-deterrent product with a relatively stable market share and abuse estimates captured at baseline during the postmarket period. Larger groupings of products can also serve as comparators and can help determine secular trends.

When available, a product that has the same active moiety, but has a different abuse-deterrent property, can serve as a comparator.

²⁴ Secora A, Dormitzer C, Staffa J, and Dal Pan G. 2014. Measures to quantify the abuse of prescription opioids: a review of data sources and metrics. *Pharmacoepidemiology and Drug Safety*, 23(12):1227-37.

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7. Understanding the background rates of drug abuse is important for protocol design and interpretation of study results. A baseline assessment of the prevalence of drug abuse for formulations of the same opioid that lack abuse-deterrent properties should be conducted and the baseline time period should be justified.
8. Submissions should include the SAP. The plan should include parameter definitions, unit of analysis, model specification, power and sample size calculations, and any additional variables or predictors. Assessment of the abuse outcome measures should consider both average levels of abuse comparing pre- and post-periods to currently available product (means analysis) and trend analysis.
9. Statistical models should include variables that may affect how the product is used and also other related confounders (e.g., geographic variability and demographic characteristics).
10. Exposure and outcome measures that include self-reported assessments should be validated before the start of the study.
11. The precision of outcome measures will also influence the observational period. Outcome measures with large uncertainty (due to bias or variability) in the exposure or study variable measures, for example, may warrant longer observational periods.
12. Interim analyses are encouraged, but results should be considered tentative in light of their preliminary nature.

B. Supportive Information

Information is considered supportive if it can be used to provide additional context on societal, behavioral, and clinical aspects of abuse and abuse-deterrance. Supportive information may be qualitative or descriptive, and it may rely on sources that capture drug utilization or prescribing patterns, diversion events, attitudes and practices (e.g., tampering) of abusers and other information that may not directly be considered abuse (e.g., data concerning the street value of prescription drugs, information about drug use and misuse from social websites). Investigations that provide supportive information may also include investigations that are conducted in smaller populations or subgroups, and that while perhaps not broadly generalizable, may contribute to the totality of the evidence relating to abuse deterrence.

As is the case for formal studies, best practices for collecting and submitting supportive information are still evolving. However, below are some basic recommendations relating to supportive information.

1. Supportive information should be clearly stated, and the rationale for how the supportive information contributes to a sponsor's portfolio of abuse-related studies should be clearly identified.
2. How supportive information is representative of the population from which it is derived or sampled should be clearly described.

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3. How the exposure and outcome are measured should be clearly described along with the relationship between the outcomes measured and the primary outcomes of interest: misuse, abuse, addiction, overdose, and death.
4. Collections of supportive information that include populations of particular interest or geographically diverse settings is strongly encouraged. Overlapping geographic areas between formal and supportive information should be considered.

VI. LABELING

Including information about a product's abuse-deterrent properties in labeling is important to inform health care professionals, the patient community, and the public about a product's abuse potential. Accordingly, FDA encourages sponsors to propose labeling that sets forth the results of in vitro, pharmacokinetic, clinical abuse potential and formal postmarket studies and appropriately characterizes the abuse-deterrent properties of a product.

There are several important concepts about the state of the science of pre- and postmarket studies of abuse deterrence that should be considered as these are reflected in labeling. First, as stated earlier in the guidance, abuse-deterrent does not mean abuse-proof. Therefore, labeling should reflect a product's abuse-deterrent properties, as supported by the data, but should include a caveat that abuse is still possible. Next, premarket studies are intended to demonstrate properties that are predictive of a meaningful abuse-deterrent effect for a particular route of administration. FDA has limited data correlating the abuse-deterrent properties of certain opioid drug products, as demonstrated by premarket studies, with the impact of those properties on abuse or adverse events associated with abuse in the post-approval setting. Even though postmarket studies have the potential to demonstrate such effects, the findings of postmarket studies are not available at the time of initial product approval. Labeling should reflect the predictive quality of premarket studies and include results of relevant completed postmarket studies.

When premarket data show that a product's abuse-deterrent properties can be expected to result in a meaningful reduction in that product's abuse, these data, together with an accurate characterization of what the data mean, should be included in product labeling.²⁵ When postmarket data become available that demonstrate a meaningful reduction in abuse by one or more routes of administration, these data should be added to the product labeling. However, if these postmarket data fail to confirm that the abuse-deterrent properties result in a reduction in abuse, or demonstrate a shift in routes of abuse that represent a greater risk (e.g., a shift from oral and nasal abuse to intravenous abuse), FDA may determine that labeling revisions are needed.

Labeling language regarding abuse deterrence should describe the product's specific abuse-deterrent properties as well as the specific routes of abuse that the product has been developed to deter. For example, a formulation that limits an abuser's ability to crush a tablet and to extract the opioid can be described as limiting manipulation for the purpose of snorting or injection if

²⁵ Abuse-deterrence information in labeling should be presented in the DRUG ABUSE AND DEPENDENCE section under 9.2 Abuse.

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the data support such a statement. For this characterization to be accurate and not misleading, however, appropriate caveats are likely to be necessary as described above. For example, a product's labeling should explain that the product's abuse-deterrent properties only make abuse more difficult, not impossible, and that these properties provide no deterrence against other potential forms of abuse.

As noted at the outset of this guidance, FDA will take a flexible, adaptive approach to the evaluation and labeling of abuse-deterrent opioid products. FDA expects sponsors to update their formulations to take advantage of technological improvements and further expects to allow labeling statements related to abuse deterrence commensurate with those advances.

Furthermore, FDA expects sponsors to compare their formulations against approved abuse-deterrent versions of the same opioid. The comparisons should be based on the relevant categories of testing. For instance, if a proposed product is less resistant to manipulation than an approved product, the proposed product may not be eligible for labeling regarding abuse-deterrent properties.

FDA is concerned that, with time, abusers may adapt to abuse-deterrent technologies and discover methods to defeat them. If and when abusers can overcome a technology such that it no longer has a meaningful effect in deterring abuse, FDA may require labeling revisions.

As discussed below, the nature of information in labeling on abuse deterrence for a particular product will depend on the types of studies performed and the result of those studies. Because it cannot provide specific guidance on the magnitude of effect that would be sufficient to support each type of claim, FDA will assess the appropriateness of all proposed labeling statements about abuse deterrence based on the data provided.

Information describing the results of the evaluation of abuse-deterrent properties can be used to support labeling statements based on the three premarket categories (i.e., in vitro data, pharmacokinetic data, and clinical abuse potential studies) and the fourth category (postmarket data) once it is available.

The data necessary to support abuse-deterrent labeling will depend on the characteristics of the product that impart the abuse deterrence and the route of abuse. In general, most abuse-deterrent information included in product labeling will be based on data from more than one category.

Key elements of the study design and conduct should be summarized in the product labeling. Category 1 studies can be described in general terms to avoid creating a *road map* for defeating the product's abuse-deterrent properties. However, the design, conduct, and results of Category 2 and 3 studies should be described in sufficient detail, including the primary outcome measure data from Category 3 studies, to support clear labeling regarding a product's abuse-deterrent properties.

The following are examples of information for inclusion in labeling for different types of abuse-deterrent effects based on various types of premarket studies performed.

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- Category 1

For this product, in vitro data demonstrated that an abuse-deterrent product cannot be crushed and dissolved or extracted in a small volume of solution suitable for injection. In this case, Category 1 in vitro data may be sufficient to support a statement in labeling about abuse deterrence for the intravenous route of abuse (See Section IV Premarket Studies). Possible labeling text:

In vitro physical and chemical tablet manipulation studies were performed to evaluate the ability of different extraction methods to defeat the formulation. Results support that Tradename resists crushing, breaking, and dissolution using a variety of tools and solvents and retains some extended-release properties despite manipulation.

These in vitro data demonstrate that Tradename has physical and chemical properties that are expected to deter intravenous abuse. However, abuse of this product is still possible by the oral and nasal routes.

- Category 1 and Category 2

For this product, in vitro and pharmacokinetic data from study of the oral and nasal routes of administration demonstrated that no changes occurred in the extended-release properties of the opioid after crushing or dissolution in a variety of solvents. These data may be sufficient to support statements in labeling about abuse deterrence for the nasal and intravenous routes of abuse. Possible labeling text:

In vitro physical and chemical tablet manipulation studies were performed to evaluate the ability of different extraction methods to defeat the formulation, and pharmacokinetic studies of the oral and intranasal routes were performed to determine the effect of manipulation on drug release. Results support that Tradename resists crushing, breaking, and dissolution using a variety of tools and solvents and retains its extended-release properties despite manipulation.

The in vitro data demonstrate that Tradename has physical and chemical properties that are expected to deter oral, nasal and intravenous abuse. However, abuse of intact product is still possible by the oral route.

- Category 2 and Category 3

For this product, pharmacokinetic and clinical abuse potential studies demonstrated the release of an antagonist from an opioid and antagonist combination product following crushing and that the presence of the antagonist resulted in less drug liking compared to a similar amount of opioid alone when administered by the oral and intranasal routes. In

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addition, an additional clinical abuse potential study simulating intravenous abuse using the amounts of opioid and antagonist found to be released from the crushed product also demonstrated reduced drug liking.

The pharmacokinetic data demonstrate that crushing Tradename results in the simultaneous release and rapid absorption of opioid and antagonist. These data along with the results from oral and intranasal clinical abuse potential studies and a clinical abuse potential study of intravenous opioid and antagonist to simulate crushed Tradename indicate that Tradename has properties that are expected to deter abuse via the oral, intranasal, and intravenous routes. However, abuse of Tradename by these routes is still possible.

All of these statements based on Categories 1, 2, or 3 testing should be followed by a statement that data from laboratory and clinical studies may not fully predict abuse potential in the post-approval setting.

As discussed in Section V, postmarket data from a variety of sources can demonstrate that a product's abuse-deterring properties result in persistent and relevant abuse deterrence. These data can result from appropriately designed, conducted, and analyzed formal postmarket studies and from supportive information on the abuse of the product.

FDA is currently considering formal studies plus a variety of supportive information (e.g., data concerning the street value of prescription drugs) as sources that may be acceptable to provide evidence that a product's formulation has had an actual impact on reducing its abuse. FDA anticipates that data from some or all three of the premarket categories along with data from postmarket studies (including both formal studies and supportive information) would be needed to support a statement in labeling that the product has been shown to reduce abuse. The combined results from all of these studies would be described in the product labeling, including specific study designs, conduct, analyses, and study data.

An example of labeling for a product with evidence of a reduction in abuse is:

These data demonstrated a reduction in the abuse of Tradename in the community setting compared to the levels of abuse, overdose, and death that occurred when only formulations of the same opioid without abuse-deterring properties were available. This reduction in abuse appears to be attributable to the product's formulation, which deters abuse by injection or snorting of the manipulated product. However, such abuse of this product is still possible, and the product's abuse deterrence properties do not deter abuse associated with swallowing the intact formulation.

VII. ADDITIONAL RESEARCH NEEDS

As discussed above, the science of abuse deterrence is relatively new. Both the technologies involved and the analytical, clinical, and statistical methods for evaluating those technologies are

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rapidly evolving. For these reasons, FDA will take a flexible, adaptive approach to the evaluation and labeling of potentially abuse-deterrent opioid products. Additionally, there is considerable room for additional scientific work that could advance the development and assessment of abuse-deterrent products. In particular, FDA encourages additional research on the following topics:

- The quantitative link between changes in the pharmacokinetics of opioids in different formulations and results of a clinical abuse potential study with those same formulations.
- The best assessment methods to employ when analyzing a clinical study of abuse potential.
- The quantitative link between the outcomes from a clinical study of abuse potential comparing formulations and the effect on those same formulations on abuse in the community.
- Further understanding of the best study methods to employ to assess the effect of a product with abuse-deterrent properties on the rates of abuse in the community.
- Development of a communication tool (e.g., a simple graph or chart) to inform prescribers of the relative impact the product has on the different routes of abuse.

Progress on these topics could facilitate the ability of sponsors to propose and FDA to approve labeling that would give a more complete picture of the anticipated effect of products with abuse-deterrent properties. Ultimately, progress in these areas could facilitate product development by reducing the amount of information that is needed to accurately assess a product with abuse-deterrent properties and predict its impact on abuse in the community.

11.3. Guidance for Industry: General Principles for Evaluating the Abuse Deterrence of Generic Solid Oral Opioid Drug Products

General Principles for Evaluating the Abuse Deterrence of Generic Solid Oral Opioid Drug Products Guidance for Industry

**U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)**

**November 2017
Generics**

General Principles for Evaluating the Abuse Deterrence of Generic Solid Oral Opioid Drug Products

Guidance for Industry

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**U.S. Department of Health and Human Services
Food and Drug Administration
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General Principles for Evaluating the Abuse Deterrence of Generic Solid Oral Opioid Drug Products Guidance for Industry¹

This guidance represents the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA office responsible for this guidance as listed on the title page.

I. INTRODUCTION

This guidance is intended to assist a person who plans to develop and submit an abbreviated new drug application (ANDA) (hereinafter potential ANDA applicant) to seek approval of a generic version of a solid oral opioid drug product that references an opioid drug product with abuse-deterrent properties described in its labeling. The guidance recommends studies, including comparative in vitro and pharmacokinetic (PK) studies, that the potential ANDA applicant should conduct and submit to FDA in an ANDA to demonstrate that a generic solid oral opioid drug product is no less abuse deterrent than its reference listed drug (RLD) with respect to all potential routes of abuse.

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

Prescription opioid analgesics are an important component of modern pain management. However, abuse and misuse of these drug products have created a serious and widespread public health problem. One potentially important step toward the goal of creating safer opioid analgesics has been the development of opioid drug products with abuse deterrent properties. FDA considers development of these products a high public health priority.

¹ This guidance has been prepared by the Office of Generic Drugs, with the assistance of the Office of Pharmaceutical Quality, in the Center for Drug Evaluation and Research at the Food and Drug Administration.

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On April 1, 2015, FDA published in the *Federal Register* a notice of availability for its final guidance, *Abuse-Deterrent Opioids — Evaluation and Labeling* (80 FR 17765).² For purposes of that guidance, “abuse-deterrent properties” are defined as those properties shown to meaningfully **detter** abuse, even if they do not fully **prevent** abuse. The term *abuse* is defined in that guidance as the intentional, nontherapeutic use of a drug product or substance, even once, to achieve a desired psychological or physiological effect.³ Abuse is not the same as *misuse*, which refers to the intentional therapeutic use of a drug product in an inappropriate way and specifically excludes the definition of abuse.⁴ Because opioid drug products must, in the end, be able to deliver the opioid to the patient, there may always be the potential for some abuse of these products. Further, products with abuse-deterrent properties do not prevent addiction; opioid analgesics, even when taken as recommended, can result in addiction.

It is important that less costly generic versions of opioids that reference RLDs whose labeling describes abuse-deterrent properties are available to ensure access to safe and effective analgesics for patients who need them. However, it is also important that the availability of such generics does not exacerbate the public health problems associated with opioid abuse. Where abuse-deterrent properties are described in the labeling of an RLD, marketing a generic version of the RLD that is less abuse deterrent could lead opioid abusers to preferentially seek out and abuse such easier-to-abuse generics.

The *Abuse-Deterrent Opioids — Evaluation and Labeling* guidance describes seven categories of abuse-deterrent technologies — physical/chemical barriers, agonist/antagonist combinations, aversion, delivery system, new molecular entities (NMEs) and prodrugs, combinations, and novel approaches. This guidance focuses on the general principles for developing and evaluating the abuse deterrence of generic solid oral opioid drug products formulated to incorporate physical or chemical barriers, agonist/antagonist combinations, aversive agents, or a combination of two or more of these technologies. It does not provide testing recommendations for generic versions of opioid drug products incorporating other technologies (i.e., delivery system, NME/prodrug, or novel approaches), but FDA may provide such testing recommendations in future product-specific guidance. Further, FDA will continue to assess the state of science and, as novel technologies develop, will address them by issuing additional guidance, as appropriate.

III. ABUSE DETERRENCE OF GENERIC SOLID ORAL OPIOID DRUG PRODUCTS

For FDA to approve an ANDA, the Agency generally must find, among other things, that the generic drug⁵ has the same active ingredient(s), conditions of use, dosage form, route of

² For the most recent version of any guidance referenced in this document, check the FDA Drugs guidance web page at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>.

³ Smith SM, Dart RC, Katz NP, et al. Classification and definition of misuse, abuse, and related events in clinical trials: ACTTION systematic review and recommendations. Pain 2013;154:2287-2296.

⁴ Ibid.

⁵ Throughout this guidance, we use the term *generic drug* to refer to a new drug product described in an ANDA submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 355(j)).

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administration, strength, and (with certain permissible differences) labeling as the RLD; it is bioequivalent to the RLD; the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of the drug are adequate to assure and preserve its identity, strength, quality, and purity; and the inactive ingredients and composition of the generic drug are not unsafe under the conditions of use prescribed, recommended, or suggested in the labeling.⁶

FDA considers a generic drug to be therapeutically equivalent to its RLD when certain conditions are met. *Therapeutic equivalents* are approved drug products that are pharmaceutical equivalents for which bioequivalence has been demonstrated and that can be expected to have the same clinical effect and safety profile.⁷ With certain limitations, FDA believes that products classified as therapeutically equivalent can be substituted with the full expectation that the substituted product will produce the same clinical effect and safety profile as the prescribed product/RLD.⁸

When a potential ANDA applicant develops a generic solid oral opioid drug product, the applicant should review the approved labeling for the RLD, particularly the information presented in the DRUG ABUSE AND DEPENDENCE section under 9.2 *Abuse*. If the summary in section 9.2 indicates that FDA has concluded that the product has properties that are expected to (or have been shown through postmarketing studies or trials to) deter abuse, in addition to other testing that may be needed to support the ANDA, the potential ANDA applicant should evaluate its proposed generic drug to show that it is no less abuse deterrent than the RLD with respect to **all** of the potential routes of abuse.⁹ This will ensure the generic drug is no less abuse deterrent than the RLD with respect to all potential routes of abuse and minimize the risk of shifting abuse to other, potentially more dangerous, routes.

The data from in vitro and in vivo studies conducted to evaluate the abuse deterrence of a proposed generic product should be included in Module 3.2.P.2 and Module 5, respectively, of the Common Technical Document in an ANDA submission.¹⁰

FDA intends to consider the totality of the evidence when evaluating the abuse deterrence of a generic solid oral opioid drug product. That is, FDA intends to consider all of the evidence presented in the ANDA including, but not limited to, study type, methodological and design quality, number of studies of each type, sample sizes, relevance of the evidence, replication of results, and overall consistency of the evidence.

⁶ See section 505(j)(2)(A) and (j)(4) of the FD&C Act.

⁷ See 21 CFR 314.3(b).

⁸ *Approved Drug Products with Therapeutic Equivalence Evaluations* (the Orange Book), preface at vii.

⁹ For questions related to evaluating an RLD's abuse deterrence, the potential ANDA applicant may seek the Agency's input through submission of controlled correspondence to the Office of Generic Drugs. See FDA's guidance for industry on *Controlled Correspondence Related to Generic Drug Development*.

¹⁰ For additional information regarding the information that should be provided in an ANDA submission, refer to the draft guidance for industry, *ANDA Submissions — Content and Format of Abbreviated New Drug Applications*.

IV. GENERAL PRINCIPLES FOR EVALUATING THE ABUSE DETERRENCE OF GENERIC SOLID ORAL OPIOID DRUG PRODUCTS

In this guidance, a proposed generic solid oral opioid drug product is referred to as “Test (T) product” and its respective RLD as “Reference (R) product.” If the labeling for R product does not describe any abuse-deterrent properties, the testing recommendations in this guidance are not applicable. Where the labeling for R product describes properties expected to deter abuse, a comparative evaluation of the abuse deterrence of T product relative to R product for all potential routes of abuse should be conducted according to the following general principles:

- **Tier-based approach to testing.** FDA recommends that potential ANDA applicants follow a tier-based approach to efficiently compare a T product to its R product and limit the number of tests required for evaluating the abuse deterrence of T product. A *tier* refers to manipulations of similar complexity, difficulty, and effort that may be used by an abuser to release the opioid drug substance. Each subsequent tier increases the complexity, difficulty, or effort of manipulation that may be used. Thus, this tier-based approach allows for hierarchical testing, evaluating abuse-deterrent properties under progressively more challenging conditions.
- **Performance-based evaluation of abuse deterrence.** The evaluation of the abuse deterrence of T product should be based on its performance relative to R product. The proposed generic drug need not have the same formulation design as R product. The evaluation of the abuse deterrence of T product for each potential route of abuse should be based on the potential ANDA applicant’s best understanding of the abuse deterrence of R product for that route, the particular potential route of abuse being evaluated, and the use of specific measures meaningful to the evaluation of abuse by that route. For example, the measure that is expected to be the most meaningful for evaluation of abuse by injection is the percentage of opioid drug substance extracted from the product under various test conditions (see Appendices 1 and 3).
- **Most effective manipulation.** FDA recommends that a potential ANDA applicant identify the most effective manipulation conditions for T and R products before comparing them. Appendix 1 provides recommendations for physical manipulations that may be used to evaluate the abuse deterrence of solid oral opioid drug products and recommendations for selecting the most effective physical manipulation to use on the drug products tested in each relevant tier.
- **Sample selection after physical manipulation.** A potential ANDA applicant should select an appropriate sample before conducting comparative in vitro studies. At a minimum, the two extreme forms of a drug product (i.e., the intact and most effectively manipulated form) should be selected for evaluation in each relevant tier. Further recommendations regarding sample size are discussed in section VIII.
- **Comparing T and R products in extraction studies.** FDA recommends that a potential ANDA applicant conduct extraction studies to assess the particular

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vulnerabilities of T and R products to inform the comparison of their abuse deterrence. Appendix 1 provides recommendations for extraction studies. For each solvent within a given tier, the potential ANDA applicant should first identify whether the most effectively manipulated R product has an observable reduction in drug extraction. If the drug extraction of R product is greater than or equal to 50 percent in 30 minutes in any solvent within the tier, R product is considered to have no abuse deterrence for purposes of that tier of testing, and no further testing to compare T and R products is recommended. Otherwise, the most effectively manipulated T product should be compared to the most effectively manipulated R product for each solvent within a tier. Then, the maximum percent extraction of opioid drug substance from T product should be compared with the maximum percent extraction of opioid drug substance from R product in each solvent.

- **Statistical comparison of T and R products.** Section VIII provides general recommendations for conducting statistical analyses.

The general principles outlined in this section are applicable to all generic solid oral opioid drug products within the scope of this guidance. This testing is in addition to other testing that may be needed to support ANDA approval. FDA may issue product-specific guidances, as appropriate, that provide more detailed recommendations for conducting in vitro testing, PK testing, or other studies or may issue guidances that provide more detailed recommendations for conducting testing to evaluate specific abuse-deterrent technologies.

Potential ANDA applicants may pose questions regarding evaluation of the abuse deterrence for a generic solid oral opioid drug product through FDA's pre-ANDA program. The goals of the pre-ANDA program are to clarify regulatory expectations for prospective applicants early in the development process, assist applicants in developing complete submissions, promote a more efficient and effective ANDA review process, and reduce the number of review cycles required to obtain ANDA approval, particularly for complex products. FDA considers abuse-deterrent opioids to be products that fall within the definition of "complex product."¹¹ The pre-ANDA program provides for, among other things, submission of controlled correspondence and requests for formal meetings between FDA and applicants on complex generic drug development issues.¹²

V. ROUTES OF ABUSE

If the summary in section 9.2 of the RLD labeling indicates that FDA has concluded that the RLD has properties that are expected to (or have been shown through postmarketing studies or trials to) deter abuse, in addition to other testing that may be needed to support an ANDA,

¹¹ *Complex product* is defined in the GDUFA Reauthorization Performance Goals and Program Enhancements Fiscal Years 2018-2022 (commonly referred to as the GDUFA II Goals letter), which can be found at <https://www.fda.gov/downloads/ForIndustry/UserFees/GenericDrugUserFees/UCM525234.pdf>. Among other things, *complex product* generally includes "...products where complexity or uncertainty concerning the approval pathway or possible alternative approaches would benefit from early scientific engagement."

¹² See FDA's guidances for industry *Controlled Correspondence Related to Generic Drug Development* and *Formal Meetings Between FDA and Applicants of Complex Generic Drug Products under GDUFA*.

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an ANDA applicant should evaluate the abuse deterrence of its proposed generic solid oral opioid drug product for all of the potential routes of abuse:

- **Ingestion (oral route)**—evaluate oral bioavailability of physically manipulated or chewed products, as described in section VII and Appendix 2.
- **Injection (parenteral route)**—evaluate the extractability and syringeability of intact and manipulated products, as described in Appendix 3.
- **Insufflation (nasal route)**—evaluate the nasal bioavailability and pharmacodynamic (PD) effects (i.e., human abuse potential) of manipulated and insufflated products, as described in section VII and Appendix 4.
- **Smoking (inhalation route)**—evaluate the ability to sublime intact and manipulated products, as described in Appendix 5.

VI. COMPARATIVE IN VITRO STUDIES

FDA recommends that potential ANDA applicants follow a tier-based approach to efficiently compare the abuse deterrence of T product to R product in in vitro studies. Appendix 1 provides recommendations for physical manipulations that may be used to evaluate the abuse deterrence of solid oral opioid drug products and recommendations for selecting the most effective physical manipulation to use on the drug product tested in the tiers. In addition, Appendix 1 provides recommendations for extraction studies using different levels of solvents to assess the particular vulnerabilities of T and R products to inform the comparison of their abuse deterrence.

FDA recommends the following levels of solvents be used in different tiers of comparative in vitro extraction studies (Appendix 1):

- Level 1 solvent: deionized water
- Level 2 solvents: commercially available food-grade vinegar, 0.2% baking soda solution, 40% ethanol, and carbonated drink
- Level 3 solvents: 100% ethanol, 100% isopropyl alcohol, acetone, 0.1 N HCl, and 0.1 N NaOH

Potential ANDA applicants may use other solvents in addition to those described above or a combination of solvents and are encouraged to seek the Agency's input on additional testing suitable for product-specific development.

A potential ANDA applicant seeking approval of more than one strength of a generic solid oral opioid drug product should evaluate and compare T product against R product for each of the strengths in any in vitro study(ies). Alternatively, the potential ANDA applicant should provide supportive data to demonstrate compositional proportionality across different strengths of T and R products or other justification as may be appropriate for not conducting

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studies to evaluate T product against R product for all strengths in the in vitro studies. When such justification is provided, a bracketing design covering the extremes of the ratios of opioid drug substance to excipients that contribute to the abuse deterrence should be applied to in vitro evaluation studies.¹³

VII. COMPARATIVE IN VIVO STUDIES

Comparative PK Studies

PK studies to evaluate the abuse deterrence of T product in comparison to R product should be conducted in cases in which no reliable in vitro testing methodologies exist or when in vitro testing methodology is overly sensitive or cannot adequately assess the abuse deterrence of T product relative to R product. For example, PK studies may be recommended to compare the abuse deterrence of T and R products for the nasal and oral routes because no reliable in vitro testing currently exists that can adequately assess abuse deterrence by those routes. The potential ANDA applicant may seek the Agency's input on the PK study design before conducting the study. FDA's recommendations for conducting comparative PK studies for various routes of abuse follow.

- **Nasal PK study:** If in vitro testing suggests that T product is no less resistant to physical manipulation than R product and both T and R products can be pulverized to a particle size range that is considered safe and tolerable for human insufflation studies, the Agency generally recommends that a nasal PK study be conducted using the same dose that was used in in vitro testing to evaluate the nasal abuse deterrence of the R product. A potential ANDA applicant should characterize the particle size distribution of physically manipulated T and R products used in the nasal PK study using an appropriate procedure. A nasal PK study should be conducted in recreational opioid users. The nasal PK study should incorporate naltrexone or other opioid antagonist to block the PD effects of the opioids except for the agonist/antagonist combination products. The recommended PK parameters for the opioid drug substance and any metabolites (if recommended for measurement in the product-specific guidance) include maximum concentration (C_{\max}), time to maximum concentration (T_{\max}), and area under the curve ($AUC_{(0-t)}$ and $AUC_{(0-\infty)}$). A potential ANDA applicant should also determine the partial AUCs (p-AUCs), e.g., in the case in which there is a clear relationship between the truncated partial area in the PK profiles at specific time points and a clinically relevant PD measure (e.g., likability or take-drug-again).
- **Oral PK study:** FDA recommends an oral PK study (e.g., chewed) be conducted on manipulated products if the summary in section 9.2 of the RLD labeling indicates that FDA has concluded that the product has properties that are expected to deter abuse by the oral route (e.g., Drug X is expected “to reduce . . . oral abuse when chewed.”) or FDA otherwise recommends such a study in product-specific guidance. Such studies

¹³ For additional information regarding bracketing design, refer to the guidance for industry, *Bioequivalence Studies with Pharmacokinetic Endpoints for Drugs Submitted Under an ANDA*.

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should be designed to compare the PK profile of the orally administered T product to that of the R product when physically manipulated (e.g., cut, grated, or milled) or chewed. A potential ANDA applicant should ensure that a suitable level of physical manipulation(s) or chewing has been applied to both T and R products to achieve the maximum percent extraction of opioid drug substance for T product and the maximum percent extraction of opioid drug substance for R product. For an oral PK study of physically manipulated products, T and R products should be physically manipulated (e.g., cut, grated, or milled) into a particle size range that can discriminate between T product's and R product's ability to deter abuse. For an oral chewing PK study, patient-relevant chewing conditions (e.g., 10 minutes) should be identified.

Oral PK studies should compare the rate and extent of absorption of physically manipulated or chewed and ingested drug products in healthy volunteers. Oral PK studies should incorporate naltrexone or other opioid antagonist to block the PD effects of the opioids except for the agonist/antagonist combination products. The recommended PK parameters for the opioid drug substance and any metabolites (if recommended for measurement in the product-specific guidance) include C_{max} , T_{max} , $AUC_{(0-t)}$, and $AUC_{(0-\infty)}$. A potential ANDA applicant should also determine p-AUCs, e.g., in the case in which there is a clear relationship between the truncated partial area in the PK profiles at specific time points and a clinically relevant PD measure (e.g., likability or take-drug-again).

- **Agonist/antagonist combination:** For any agonist/antagonist combination product, both the agonist and the antagonist, along with their metabolites (if recommended for measurement in the product-specific guidance), should be measured in a PK study. Appropriate bioanalytical methods should be developed to measure the concentration of both the agonist and the antagonist in the PK study. The oral PK study should be conducted to demonstrate that minimal antagonist absorption occurs when fully intact agonist/antagonist combination products are orally administered. When an oral PK study on the physically manipulated or chewed agonist/antagonist combination product is recommended, the oral PK study should compare both agonist and antagonist levels from manipulated T and R products to confirm that the antagonist is sequestered within the formulation and released upon physical manipulation or chewing followed by oral ingestion. Appropriate methods should be used to manipulate both T and R products to obtain the maximum percent extraction of opioid drug substance for R product and the maximum percent extraction of opioid drug substance for T product, based on extraction studies (Appendix 1). In addition, if T and R products can be manipulated into fine particles (Appendix 4), the potential ANDA applicant generally should conduct a human insufflation PK study, administering physically manipulated T and R products in recreational opioid users, and measure both the agonist and the antagonist, along with their metabolites, if recommended in the product-specific guidance (Appendix 4).
- **Multiple strengths:** When PK studies are conducted to evaluate the abuse deterrence of T product in comparison to R product for approval of more than one strength of a

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proposed generic solid oral opioid drug product, the strength(s) selected for the PK studies should be based on the strength(s) used to evaluate the R product's abuse deterrence. Clinical abuse potential studies conducted to evaluate the abuse deterrence for new drug applications submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 355(b)) are generally conducted using an intermediate strength. If the labeling for the R product does not identify the strength(s) tested, FDA intends to provide recommendations in a product-specific guidance.

Other Studies

For generic drugs, comparative in vitro and PK studies generally provide sufficient evidence to demonstrate that T product is no less abuse deterrent than R product. Other studies are generally not recommended, except in certain circumstances in which such studies may be needed to establish that a generic product can rely on the finding of safety and effectiveness for the RLD. For example, where R product contains a known aversive agent and T product contains a different aversive agent, FDA may recommend that the potential ANDA applicant conduct a PD study to compare human abuse potential (e.g., willingness to take the drug again) between T product and R product. Potential ANDA applicants are encouraged to seek the Agency's input on study design before conducting such studies.

VIII. STATISTICAL ANALYSIS

Potential ANDA applicants should use inferential analyses to evaluate the abuse deterrence of T product versus R product. A non-inferiority approach should be taken when comparing T product with R product to conclude that T product is no less abuse deterrent than R product. In the analyses recommended in this guidance, a hierarchical set of null hypotheses serves as a gatekeeper for subsequent null hypotheses, evaluating the abuse deterrence of T and R products under progressively more challenging conditions. A hierarchical inferential approach is used to maintain a fixed family-wise experiment Type 1 error rate. Typically, the acceptable Type I error probability (α) will be set at 5 percent.

Tiers, defined by the complexity, difficulty, and effort of manipulations, start with the mildest set of manipulations in Tier 1. Tier 1 serves as a serial gatekeeper for the subsequent tiers. All the null hypotheses within Tier 1 should be rejected prior to testing the null hypotheses in the next tiers, which are defined by a relevant parameter describing T or R product (e.g., the percent of opioid drug substance extracted from T or R product in extraction studies) under progressively more challenging conditions. In Tier 1, all the null hypotheses are evaluated at the Type I error level of α without adjusting for the number of hypotheses; this follows from the closed testing principle.

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With tiers (sets) labeled T_1 , T_2 , T_3 , etc., and arranged hierarchically (i.e., in strictly increasing order), T_j ($j > 1$) is tested only if *all* null hypotheses in the preceding tiers have been rejected by their within-tier α -level tests. From the closed testing principle, it follows that this partially ordered procedure controls the α -level for all null hypotheses in the tiers T_1 , T_2 , T_3 , etc. (Maurer et al.¹⁴).

Dmitrienko et al.¹⁵ further generalized this hierarchical testing procedure. They proposed tree-structured gatekeeping tests that rely on a decision tree with multiple branches corresponding to multiple objectives within a tier. This approach could be used, for example, in evaluating extractability, where the effects of solvents at elevated temperature are of interest distinct from those at room temperature.

For example, to evaluate the extractability of opioid drug substance from T product and R product using this tier-based approach, a potential ANDA applicant should first find and use the most effective physical manipulation for R product and evaluate the percent extraction of opioid drug substance from R product in each solvent within the tier. If at 30 minutes the percent extraction of opioid drug substance from R product is statistically less than 50 percent (Type I error = 0.05) in all solvents for the extraction studies, the potential ANDA applicant should evaluate whether or not the maximum percent extraction of opioid drug substance from T product in each solvent is greater than or equal to maximum percent extraction of opioid drug substance from R plus 10 percent in the same solvent, 10 percent being an absolute margin (e.g., if the percent of opioid drug substance extracted from R product is 25 percent, the percent extracted from T product must be less than 35 percent).

When abuse deterrence is evaluated by comparing the percent of opioid drug substance extracted from a product, if the percent of opioid drug substance extracted from T product is statistically greater than or equal to the percent of opioid drug substance extracted from R plus 10 percent in any of the solvents within the tier, then T product is considered to be less abuse deterrent than R; thus, T product will not be tested further. In contrast, if the percent of opioid drug substance extracted from T product is statistically less than the percent of opioid drug substance extracted from R plus 10 percent in all the solvents within the tier, the abuse deterrence of T product is then evaluated in the next tier. The percent of opioid drug substance extracted from T product must be less than the percent of opioid drug substance extracted from R plus 10 percent for each set of study conditions for which it is evaluated in order to claim it is no less abuse deterrent than the corresponding R product (see Tables 1 and 2 in the appendices for more detail).

All inferential comparisons involve the mean of the measure of the abuse deterrence or a function of the mean (e.g., the mean of T product minus the mean of R product). The inferential tests used to evaluate the hypotheses are left to the discretion of the potential ANDA applicant. In general, FDA recommends conducting all in vitro tests using 6 units

¹⁴ Maurer W, Hothorn LA, Lehmacher W. Multiple comparisons in drug clinical trials and preclinical assays: A-priori ordered hypotheses. Biometrie in der Chemisch-pharmazeutischen Industrie. 1995;6:3-18.

¹⁵ Dmitrienko A, Wiens BL, Tamhane AC, Wang X. Tree-structured gatekeeping tests in clinical trials with hierarchically ordered multiple objectives. Stat Med. 2007;26(12):2465-2478.

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(e.g., tablets or capsules) of each T and R product. The potential ANDA applicant may propose a different sample size if the applicant can provide justification that such sample size allows for accurate characterization of the mean. FDA recommends that the potential ANDA applicant develop an analysis plan that has contingencies for various scenarios (e.g., data that are not normally distributed and data that are left-censored (i.e., values below the limit of quantification)).

Tables 1 and 2 found in the appendices guide potential ANDA applicants through the recommended series of study conditions and statistical analyses for extractability and abuse by smoking (sublimation), respectively. As the first step in each tier, the potential ANDA applicant should identify the most effective physical manipulations and compare R product to a constant (in the case of extractability, see Appendix 1) or R product directly to T product (in the case of sublimation). If the percent of opioid drug substance extracted from R product is less than a constant in case of extractability, the testing should continue to the second step within that tier. If, at the end of the second step, it is possible to conclude that T product is no less abuse deterrent than R product, then testing of T product should move on to the next tier. This process continues for the remaining tiers within a table until:

- The percent extraction of opioid drug substance from R product is greater than or equal to the constant in the case of extractability, in which case R product is considered to have no abuse deterrence for the route of abuse being tested; or
- The percent extraction of opioid drug substance from T product is greater than or equal to that from R plus 10 percent.

In order to show that T product is no less abuse deterrent than R product, T product should be shown to be non-inferior to R product at each tier for which it is evaluated.

IX. ADDITIONAL STUDIES

There may be instances in which the testing recommended in this guidance cannot adequately capture the complete profile for T product because of factors including, but not limited to, inclusion of novel inactive ingredients, use of new technology, and formulation design. In such instances, FDA may, as permitted under section 505(j) of the FD&C Act, request that additional studies, aside from the ones described in Appendices 2 to 5, be conducted to evaluate the abuse deterrence of T product. As new technologies emerge, FDA intends to continue adapting its recommendations for developing and evaluating generic solid oral and other opioid drug products formulated to deter abuse to help ensure access to effective analgesics for patients who need them.

APPENDIX 1: PHYSICAL MANIPULATION AND EXTRACTABILITY

Physical Manipulation

The extent to which a solid oral opioid drug product can be physically manipulated is a function of several factors including, but not limited to, tampering skills, time, and tampering resources available. This appendix describes some of the ways in which solid oral opioid drug products can be physically manipulated using readily available household equipment. There are additional ways in which products could be physically manipulated (e.g., crushing, hammering). The Food and Drug Administration (FDA) recommends that potential abbreviated new drug application (ANDA) applicants use the physical manipulation(s) most likely to be used by abusers when they conduct studies to evaluate the abuse deterrence of a specific Test (T) product.

Some of the questions that the physical manipulation evaluation should address include:

- What is the degree of difficulty of the manipulation?
- How successful is each manipulation method in achieving its goal (e.g., compromising a tablet's integrity)?
- If the structure of the dosage form is compromised, what are the size and size distribution of the resulting particles?

Physical manipulation should be used to gain an understanding of the robustness of the abuse-deterrent properties. To identify the most effective physical manipulation, potential applicants should use a relevant endpoint, which may vary based on formulation design. For example, for a tablet dosage form designed to be crush resistant, such an endpoint could be the size of the fragment after cutting, grating, or milling. In this case, the potential applicant should provide particle size distribution data to justify the selection of the manipulation method. Particle size for physically manipulated products can be analyzed using techniques including, but not limited to, photograph with scale, image analysis, sieve analysis, and laser diffraction. In addition, if deemed useful, the extraction data in deionized water of manipulated dosage forms may be used to further justify the selection of the most effective physical manipulation that will result in high extraction levels.

Manipulation by cutting

As illustrated in Figure 1 below, progressive manipulation by cutting involves:

- Cutting without thermal pretreatment: If a drug product can be cut in less than 5 minutes at room temperature (RT) into 10 or more small pieces using a knife, manipulation with thermal pretreatment (freezing or heating) is not needed.
- Cutting with thermal pretreatment: If a drug product cannot be cut at RT as described above, suitable thermal pretreatment should be developed and used.

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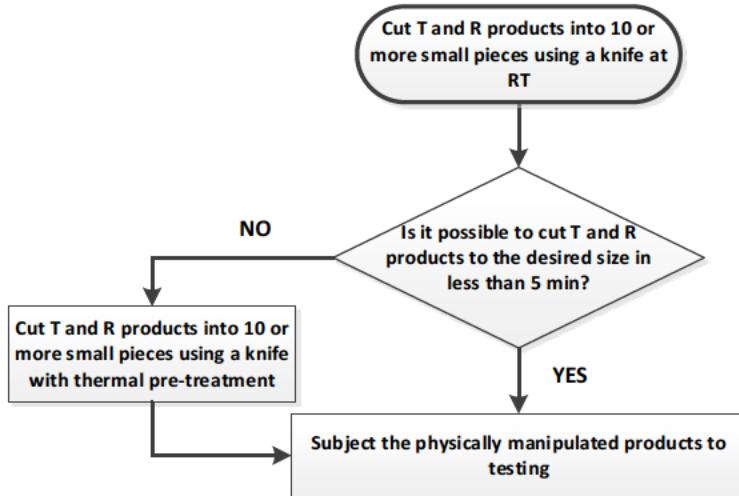


Figure 1: Physical Manipulation by Cutting for Solid Oral Opioid Drug Products

Manipulation by grating

As illustrated in Figure 2 below, progressive manipulation by grating involves:

- Grating without thermal pretreatment: If a drug product can be grated in less than 5 minutes at RT to a size less than 1 millimeter (mm) using a household grater, manipulation with thermal pretreatment (freezing or heating) is not needed.
- Grating with thermal pretreatment: If a drug product cannot be grated at RT as described above, suitable thermal pretreatment should be developed and used.

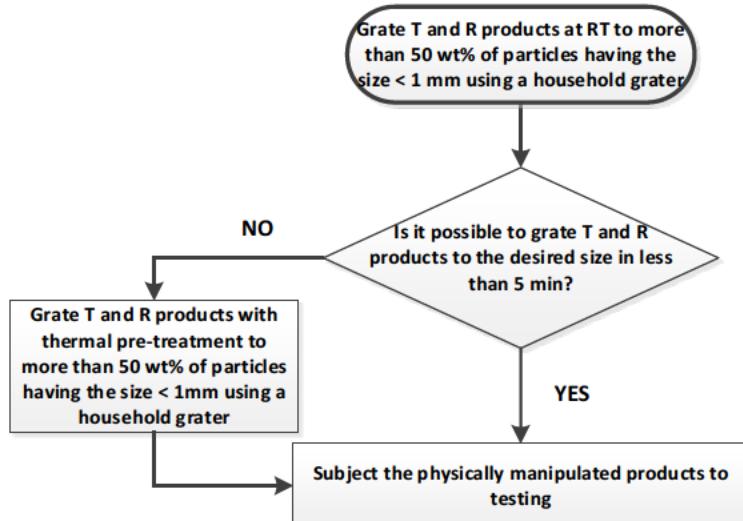


Figure 2: Physical Manipulation by Grating for Solid Oral Opioid Drug Products

Manipulation by milling

As illustrated in Figure 3 below, progressive manipulation by milling involves:

- Milling without thermal pretreatment: If a drug product can be milled in less than 5 minutes at RT to a size less than 1 mm using a household coffee grinder, manipulation with thermal pretreatment (freezing or heating) is not needed.
- Milling with thermal pretreatment: If a drug product cannot be milled at RT as described above, suitable thermal pretreatment should be developed and used.

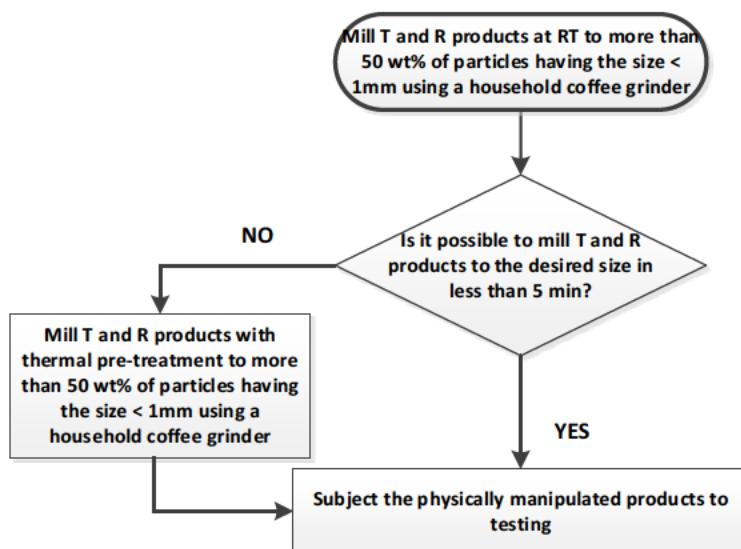


Figure 3: Physical Manipulation by Milling for Solid Oral Opioid Drug Products

Extractability

Evaluation of the extractability of physically manipulated opioid drug products

The potential ANDA applicant should conduct comparative extractability testing on T and Reference (R) products to assess the particular vulnerabilities of each product to inform the comparison of their abuse deterrence. Comparative extractability testing should be conducted on both the intact and most effectively physically manipulated (e.g., cut, grated, or milled) drug products. To conclude that T product is no less abuse deterrent than R product in terms of its extractability, the potential applicant should test the intact and physically manipulated T products and show they are no worse than the intact and manipulated R products, respectively.

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Extractability of the opioid drug substance into large volumes of water or an organic solvent may be assessed at RT¹⁶ or elevated temperature (ET).¹⁷ The focus of the extraction studies is to assess the extractability of the opioid drug substance and measure the amount of opioid drug substance available in solutions, determined experimentally by measurement of the concentration and volume of the extraction media.

The percent of opioid drug substance extracted is determined as follows: (CONC*V/labeled strength of the R product) *100, where CONC is the concentration of opioid drug substance in the extraction medium and V is the volume of the extraction solution. If R product is an agonist/antagonist combination, both the percent of opioid drug substance extracted and the ratio of percent of agonist and antagonist extracted should be determined.

Study conditions

Extractability testing should be conducted for intact and physically manipulated product at RT and ET with relevant solvents using the tiered approach. Some of the ways in which solid oral opioid drug products can be physically manipulated are described above. At a minimum, the potential ANDA applicant should compare the intact T and R products and most effectively physically manipulated T and R products.

Because different solvents could be used to extract the opioid drug substance from the opioid drug product, all solvents within relevant tiers (see section VI) should be tested to assess extractability. For example, the following range of extraction conditions can be used: extraction volume of 240 milliliters (mL), RT or ET for the relevant extraction media, duration 30 minutes, with or without stirring.

The tier-based approach for evaluating extractability is illustrated in Figure 4. The parallel tier-based approach (e.g., Tier 1 → Tier 2A → Tier 3A and Tier 1 → Tier 2B → Tier 3B) to the comparative extractability studies is based on using different levels of solvents and increasing temperature within the recommended range of study conditions.

¹⁶ U.S. Pharmacopoeia (USP) controlled room temperature (20°C to 25°C).

¹⁷ Boiling temperature of the solvents used.

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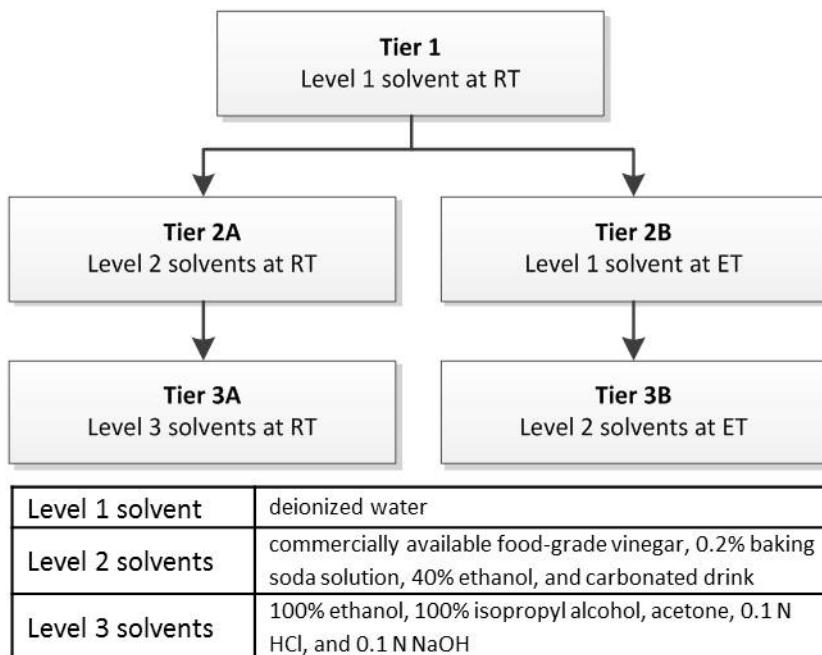


Figure 4: Parallel Tiered Approach for Determining the Extractability of Opioid Drug Substance

If the percent of opioid drug substance extracted from T product is less than that extracted from R product plus an absolute 10 percent in Tier 1, the potential ANDA applicant should conduct the extractability study in both Tiers 2A and 2B. If the percent of opioid drug substance extracted from T product is less than that from R plus an absolute 10 percent in Tier 2A, the potential ANDA applicant should proceed with the extractability study in Tier 3A. If the percent of opioid drug substance extracted from T product is less than that from R plus an absolute 10 percent in Tier 2B, the potential ANDA applicant should proceed with the extractability study in Tier 3B. Figure 5 and Table 1 guide potential ANDA applicants through the recommended series of study conditions and statistical analyses for determining extractability.

Tier 1: Extraction of intact and manipulated (e.g., cut, grated, or milled) products in Level 1 solvent at RT

Evaluate R product. A potential ANDA applicant should identify the most effective physical manipulation for R product at RT. If the percent of opioid drug substance extracted from R product using 240 mL of solvent is greater than or equal to 50 percent at 30 minutes for the intact or physically manipulated R product, R product is considered to have no abuse deterrence under this tier of testing. Therefore, no comparative testing of T product to R product is needed.

Compare T and R products. If the maximum percent of opioid drug substance extracted from R product in 240 mL of solvent is less than 50 percent in 30 minutes in the level 1 solvent, the potential ANDA applicant should compare the maximum percent of opioid drug substance extracted from the intact and most effectively physically manipulated T product to

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the maximum percent extracted from the intact and most effectively physically manipulated R product, respectively. If the maximum percent of opioid drug substance extracted from T product is less than the maximum percent of opioid drug substance extracted from R product plus an absolute 10 percent (section VIII), the potential ANDA applicant should conduct testing at the next tier.

Tier 2A: Extraction of intact and manipulated (e.g., cut, grated, or milled) products in Level 2 solvents at RT

Evaluate R product. A potential ANDA applicant should identify the most effective physical manipulation for R product at RT. If the percent of opioid drug substance extracted from R using 240 mL of solvent is greater than or equal to 50 percent at 30 minutes in any of the level 2 solvents, R product is considered to have no abuse deterrence under this tier of testing. Therefore, no comparative testing of T product to R product is needed.

Compare T and R products. If the maximum percent of opioid drug substance extracted from R product in 240 mL of solvent is less than 50 percent in 30 minutes in all level 2 solvents, the potential ANDA applicant should identify conditions (physical and thermal manipulation methods) that lead to the extraction of the maximum percent of opioid drug substance from intact and physically manipulated T products in all level 2 solvents at RT. The maximum percent of opioid drug substance extracted from T and R products in each solvent should be compared. Extractability of T and R products should be compared as described in section VIII and shown in Figure 5 and Table 1.

Tier 2B: Extraction of intact and manipulated (e.g., cut, grated, or milled) products in Level 1 solvents at ET

As shown in Table 2, the same steps described in Tier 1 (identify the study condition where extraction of opioid drug substance from T and R products is maximum, evaluate R product, and compare T and R products) should be used for testing T and R products in Tier 2B using level 1 solvents at ET.

Tier 3A: Extraction of intact and manipulated (e.g., cut, grated, or milled) products in Level 3 solvents at RT

As shown in Table 2, the same steps described in Tier 2A (identify the study condition where extraction of opioid drug substance from T and R products is maximum, evaluate R product, and compare T and R products) should be used for testing T and R products in Tier 3A using level 3 solvents at RT.

Tier 3B: Extraction of intact and manipulated (e.g., cut, grated, or milled) products in Level 2 solvents at ET

As shown in Table 2, the same steps described in Tier 2A (identify the study condition where extraction of opioid drug substance from T and R products is maximum in each solvent, evaluate R product, and compare T and R products) should be used for testing T and R products in Tier 3B using level 2 solvents at ET.

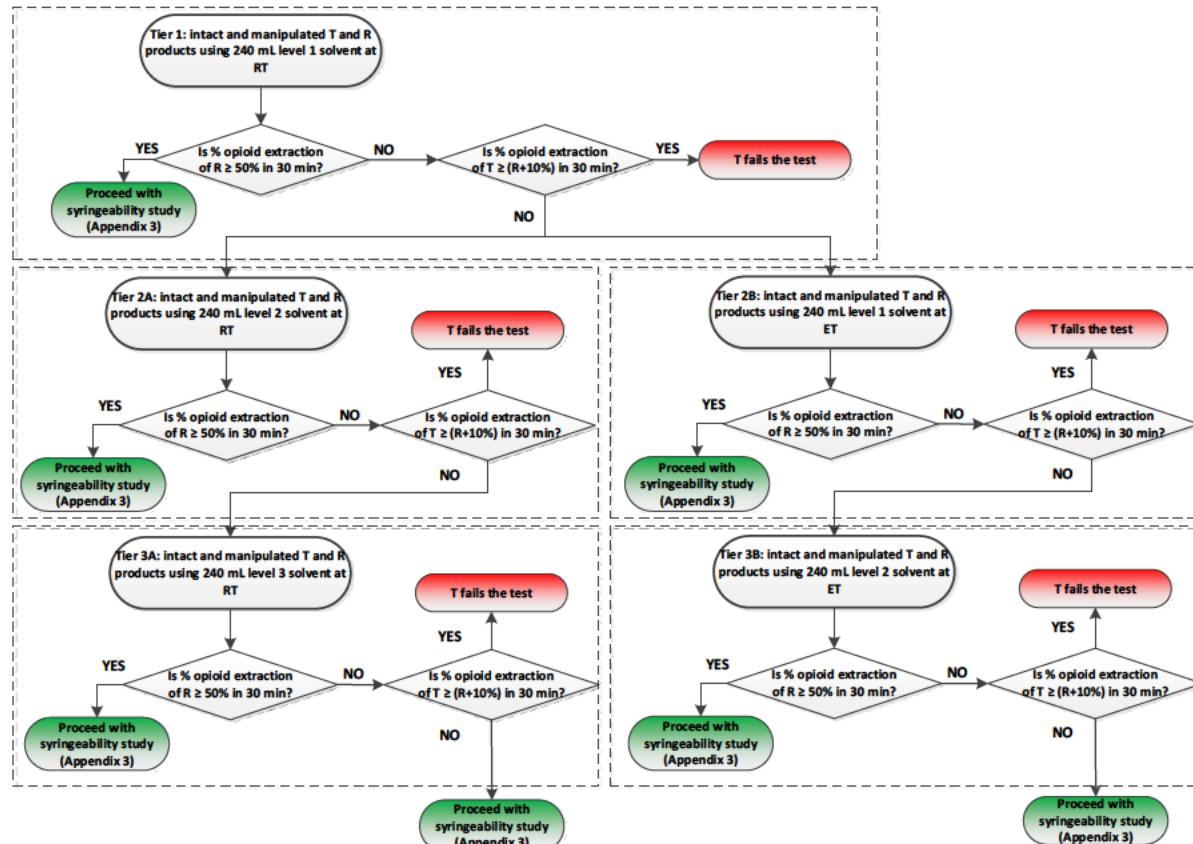


Figure 5: Decision Tree for Determining Extractability of Opioid Drug Substance (each dotted box represents one tier)

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Table 1: Statistical Evaluation of Extractability

TIER		Study Conditions 240 mL all solvents within the tier Extraction Duration 30 min		
Identify extraction study condition		$H_0: R < 50\% \text{ in 30 min}$ versus $H_1: R > 50\% \text{ in 30 min}$ If $R < 50\% \text{ in 30 min}$ <i>Conclude that less than 50% of opioid drug substance can be extracted from R product</i>		If $R \geq 50\% \text{ in 30 min}$ <i>Conclude that equal or more than 50% of opioid drug substance can be extracted from R product; no further comparative testing</i>
Evaluate T vs R at study conditions identified in this tier		$H_0: T < R+10\% \text{ in 30 min}$ versus $H_1: T \geq R+10\% \text{ in 30 min}$ If $T < R+10\% \text{ in 30 min}$ <i>Conclude that T product is no worse than R product by an amount < 10%; T product passes the study under this tier</i>	If $T \geq R+10\% \text{ in 30 min}$ <i>Conclude that T product is worse than R product by an amount \geq 10%; T product fails the study under this tier</i> CONTINUE to the next tier or STOP no further testing, if this is the last tier	STOP no further testing

Note: The measure used to evaluate extractability is the % opioid drug substance extraction, determined as follows: (CONC*V/ labeled strength of R product) *100, where CONC is the concentration of opioid drug substance in the solution, and V is the volume of the solution. 10% is applied as an absolute margin.

APPENDIX 2: ABUSE BY INGESTION (ORAL ROUTE)

Abuse by ingestion may involve orally ingesting physically manipulated (e.g., cut, grated, or milled) or chewed drug products. FDA recommends an oral PK study be conducted on physically manipulated or chewed products if the summary in section 9.2 of the RLD labeling indicates that FDA has concluded that the product has properties that are expected to deter abuse by the oral route (i.e., Drug X is expected “to reduce . . . oral abuse when chewed.”) or FDA otherwise recommends such a study in product-specific guidance.

FDA recommends a potential ANDA applicant first conduct comparative extractability studies as described in Appendix 1 to assess the particular vulnerabilities of the T and R products to inform the comparison of their abuse deterrence. If the potential ANDA applicant conducts a PK study, the study should compare the rate and extent of absorption of orally administered T and R products that are physically manipulated or chewed. The strength(s) selected for the PK study should be based on the strength(s) used to evaluate the R product’s abuse deterrence. If the upper 95 percent confidence bound of the T/R ratio for the rate and extent of oral absorption of the opioid drug substance is less than 125 percent, then T product passes the test. For agonist/antagonist combination products, T product passes the test if the lower 95 percent confidence bound of the T/R ratio for the rate and extent of oral absorption of the antagonist is greater than 80 percent. Section VII.A. outlines general recommendations for conducting oral PK studies. Alternatively, the potential ANDA applicant may rely on data from in vitro testing if such methods and data are adequate to compare the rate and extent of absorption of orally administered T and R products to evaluate whether T product is no less abuse deterrent than R product for the oral route.

APPENDIX 3: ABUSE BY INJECTION (PARENTERAL ROUTE)

Abuse by injection usually involves extraction of opioid drug substance from intact or physically manipulated (e.g., cut, grated, or milled) opioid drug products at RT and ET in small volumes of water followed by injection using a syringe. To evaluate abuse deterrence for the parenteral route, a potential ANDA applicant should measure the amount of opioid drug substance available for injection after evaluating whether or not the solvent used can be parenterally administered in humans or evaporated for reconstitution. The amount is determined by the opioid drug substance concentration in a solvent such as water (extractability), the volume that can be drawn into a syringe, and the volume that can be expelled from the syringe's needle (syringeability).

The potential ANDA applicant should note that comparative extractability and syringeability testing should be conducted with intact and physically manipulated (e.g., cut, grated, or milled) drug products. To evaluate whether T product is no less abuse deterrent than R product for the parenteral route of abuse, the intact and physically manipulated T products should be compared with intact and physically manipulated R products, respectively, under each applicable study condition, as described below.

The measure considered meaningful for evaluating the abuse deterrence relevant to abuse by injection is the percent of opioid drug substance extraction determined as follows: $(CONC \cdot V / \text{labeled strength of the R product}) \cdot 100$, where CONC is the concentration of opioid drug substance in the sample that can be expelled from the syringe needle, and V is the volume of the solution expelled. If R product is an agonist/antagonist combination, the ratio of the percent of opioid drug substance extraction of agonist to antagonist should be determined.

Study conditions

Syringeability testing should be conducted on the intact and manipulated T and R products in a small volume (10 mL) of each of the solvents in the relevant tier as described in Figure 6 if the maximum extraction of opioid drug substance from R product in 240 mL of solvent is equal or more than 50 percent in 30 minutes in a tier or T product successfully passes the large volume (240 mL) extraction study in all tiers (Figure 5). If the opioid drug substance can be extracted from R product in a large volume of solvent, the potential applicant should conduct comparative syringeability testing in a small volume of the same solvent. In general, FDA recommends conducting syringeability testing using a single unit of each T product and R product. If single-unit syringeability testing cannot accurately characterize the syringeability of R product, the potential ANDA applicant should conduct multiple-unit syringeability tests and justify that the number of tablets or capsules used in syringeability tests can sufficiently discriminate the comparative syringeability of T and R products. Appendix 1 describes some of the ways in which solid oral opioid drug products can be physically manipulated. For each manipulation likely to be used by abusers, T and R products should be statistically compared, as described in section VIII.

Following physical manipulation (e.g., cutting, grating, or milling), further testing of syringeability is recommended under the following range of study conditions: solvents used

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in the tier, volume 10 mL, temperature RT or ET, duration 5 to 60 minutes, and needle gauge 21 or finer. The study conditions, including extraction time, syringing time, needle gauge number, and filtering of particles, should be specified in the ANDA.

Evaluate solvents. If the solvent cannot be parenterally administered in humans or evaporated for reconstitution, no comparative syringeability testing of T product to R product is needed using that solvent. If the solvent can be administered in humans or evaporated for reconstitution, the potential ANDA applicant should compare T and R products.

Compare T and R products. The potential ANDA applicant should test the intact and manipulated T product and compare the abuse deterrence of T product to intact and manipulated R product, respectively. Then, the maximum percent of opioid drug substance extracted from T product should be evaluated to determine whether it is greater than or equal to R plus an absolute 10 percent in 30 minutes.

Figure 6 illustrates the tier-based approach for evaluating the syringeability of opioids for abuse by injection, as described above.

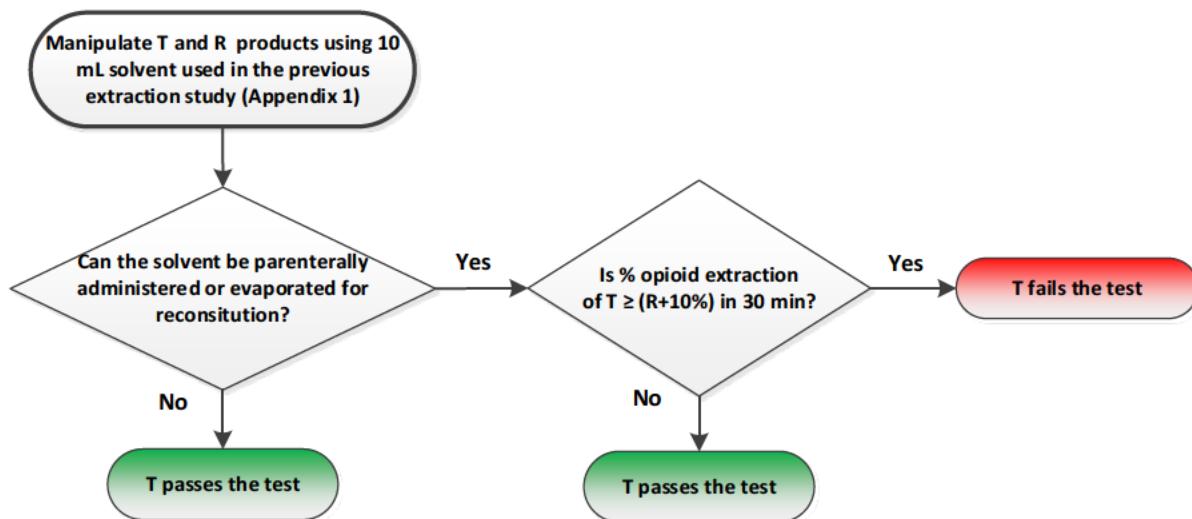


Figure 6: Decision Tree for Determining the Syringeability of Opioid to Evaluate Abuse-Deterrence Potential (abuse by injection)

APPENDIX 4: ABUSE BY INSUFFLATION (NASAL ROUTE)

Abuse by insufflation generally involves the snorting of manipulated solid oral opioid drug products. The known approaches to deterring insufflation include reducing bioavailability and reducing human abuse potential (e.g., likability or take-drug-again) of the abused product. Thus, to evaluate abuse deterrence for the nasal route of abuse, a potential ANDA applicant should test T product for reduced bioavailability and/or reduced human abuse potential.

The measure considered meaningful for in vitro evaluation of reduced bioavailability is the mass percent of fine particles (<500 micrometers (μm)) available for insufflation.

Reduced Bioavailability

Reducing the opioid drug substance available for insufflation may be accomplished by inclusion of excipients that impart hardness to the formulation and make it difficult to manipulate, retard the rate of release of the opioid drug substance from the manipulated product, or increase the size of the drug product, thereby increasing the amount of manipulated powder and proportionally decreasing the amount of opioid drug substance to be insufflated.

Consequently, the amount of opioid drug substance available following insufflation of manipulated T and R products is a function of several factors, including, but not limited to, the ease of manipulation of the drug product, the amount of manipulated product available for insufflation, the degree of effort needed for manipulation, and the rate of release of opioid drug substance from the manipulated product. Therefore, evaluation of a product's bioavailability includes measuring the size and amount of particles available for insufflation and measuring the rate and extent of absorption of manipulated T and R products following nasal administration.

The tier-based approach to the comparative studies for evaluating bioavailability of opioid drug substance when abused through the nasal route is based on the progressively more complex studies moving from in vitro studies in Tier 1 to a PK study in Tier 2. The potential ANDA applicant can propose alternative in vitro evaluation methods to assess the abuse deterrence of T products to avoid conducting a PK study if the methods provide reliable and predictive information on the PK behavior and performance of manipulated opioid drug products following insufflation.

Tier 1: Evaluation of manipulated T and R products

Identify study condition. Appendix 1 describes some of the ways in which solid oral opioid drug products can be physically manipulated. If T and R products cannot be pulverized into fine particles (<500 μm) after 5 minutes of manipulation (with or without thermal pretreatment), alternative approaches such as crushing, hammering, or grating after thermal pretreatment can be used to generate particles of size less than 500 μm .

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Evaluate T product. If the mass percent of fine particles (<500 µm) of T product is less than or equal to 10 percent, then T product is deemed unsuitable for insufflation. No comparative testing of T product to R product is needed. Otherwise, the potential applicant should evaluate R product.

Evaluate R product. R product is manipulated under the same manipulation condition. If the mass percent of fine particles (<500 µm) of R product is less than or equal to 10 percent, then R product is deemed more resistant to physical manipulation than T product for insufflation. If the mass percent of fine particles (<500 µm) of R product is greater than 10 percent, testing should proceed to Tier 2.

If both T and R products can be manipulated into fine particles with the mass percent of fine particles (<500 µm) being greater than 10 percent, FDA generally recommends conducting a comparative PK study (Tier 2) to evaluate whether a proposed generic drug deters abuse by the nasal route. Any exceptions would be provided in product-specific guidance.

Tier 2: Evaluation of manipulated and insufflated T and R products in a PK study

Identify manipulation condition. Approaches to physical manipulation of T product should be identified to achieve a particle size range that is considered safe and tolerable for human insufflation PK studies (i.e., $D_{10}>100\text{ }\mu\text{m}$ and $D_{90}<1000\text{ }\mu\text{m}$). To conduct a comparative nasal PK study, R product should be manipulated into the same particle size range using an equal or lesser amount of energy input. A potential ANDA applicant should characterize the particle size distribution of physically manipulated T and R products used in a nasal PK study using an appropriate procedure.

Compare T and R products. In section VII.A., FDA provides general recommendations for conducting nasal PK studies. The strength(s) selected for a PK study should be based on the strength(s) used to evaluate R product's abuse deterrence. If the upper 95 percent confidence bound of the T/R ratio for the rate and extent of absorption of the insufflated opioid drug substance is less than 125 percent, then T product passes the test. In addition, for agonist/antagonist combination products, T product passes the test if the lower 95 percent confidence bound of the T/R ratio for the rate and extent of absorption of the insufflated antagonist is greater than 80 percent. Otherwise, T product is considered to be less abuse deterrent than R product.

The tier-based approach to testing products for nasal bioavailability, as just described, is illustrated in Figure 7.

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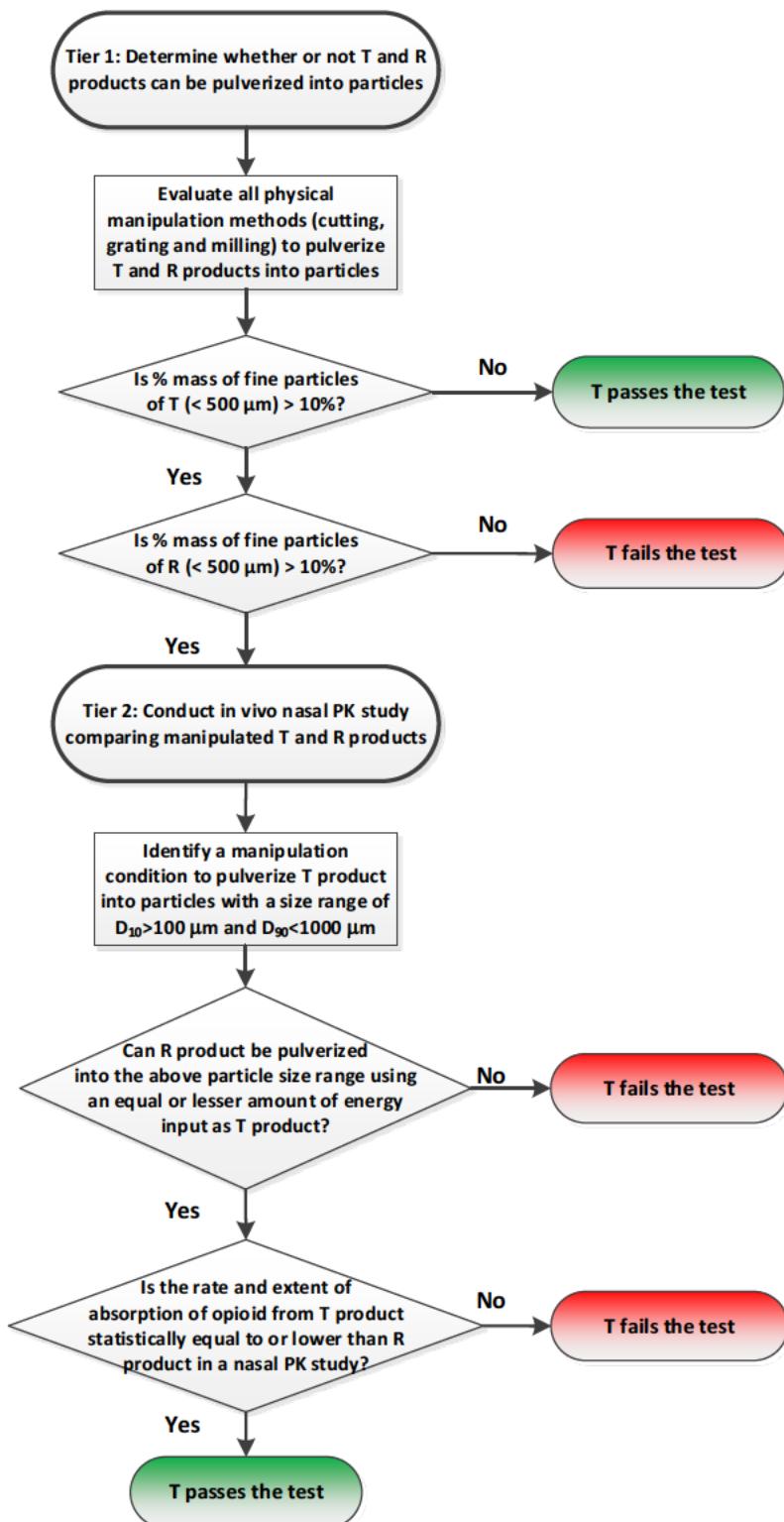


Figure 7: Decision Tree for Evaluation of Abuse Deterrence Potential (abuse by insufflation)

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Reduced Human Abuse Potential

Abuse deterrence by the nasal route may also be accomplished by addition of excipients that produce an unpleasant effect if the dosage form is manipulated and insuflated. These excipients (e.g., sodium lauryl sulfate), referred to as aversive agents, are known to cause nasal mucosal irritation. In product-specific guidance, FDA may recommend a potential applicant evaluate human abuse potential (e.g., willingness to take the drug again) if R product contains a known aversive agent.

Evaluate R product. If R product does not contain a known aversive agent in its formulation, then no comparative human abuse potential testing of T and R products is needed. If R product contains a known aversive agent, the potential applicant should evaluate T product.

Evaluate T product. If T product contains a different aversive agent than R product, the potential applicant should conduct a comparative pharmacodynamics (PD) study to determine the human abuse potential (e.g., willingness to take the drug again) of T product in comparison to R product. If T product contains the same aversive agent as R product, the potential applicant should compare availability of the aversive agent at the local sites of aversion for manipulated T and R products.

Compare T and R products with same aversive agent. If T product contains the same aversive agent and the availability of the aversive agent in T product at the local sites of aversion is not less than that of R, T product is considered to have similar abuse deterrence as R product and no further testing is needed. The availability of an aversive agent at the local sites of aversion could be based on evidence including, but not limited to, qualitative (Q1) and quantitative (Q2) formulation sameness between T and R products, in vitro methods that demonstrate equivalent performance, and PK studies to measure systemic exposure of the aversive agent. The potential ANDA applicant may propose alternative studies if the applicant can provide justification that such study allows for accurate and sensitive comparison of availability of the aversive agent at the local sites of aversion between T and R products. If the above approaches cannot confirm that the availability of the aversive agent of T product is not less than that of R product at the local sites of aversion, the potential ANDA applicant should conduct a comparative PD study to determine the human abuse potential of T product in comparison to R product. The potential ANDA applicant should discuss the study design with the Agency before conducting the study.

The proposed testing for comparison of T and R products' human abuse potential is illustrated in Figure 8.

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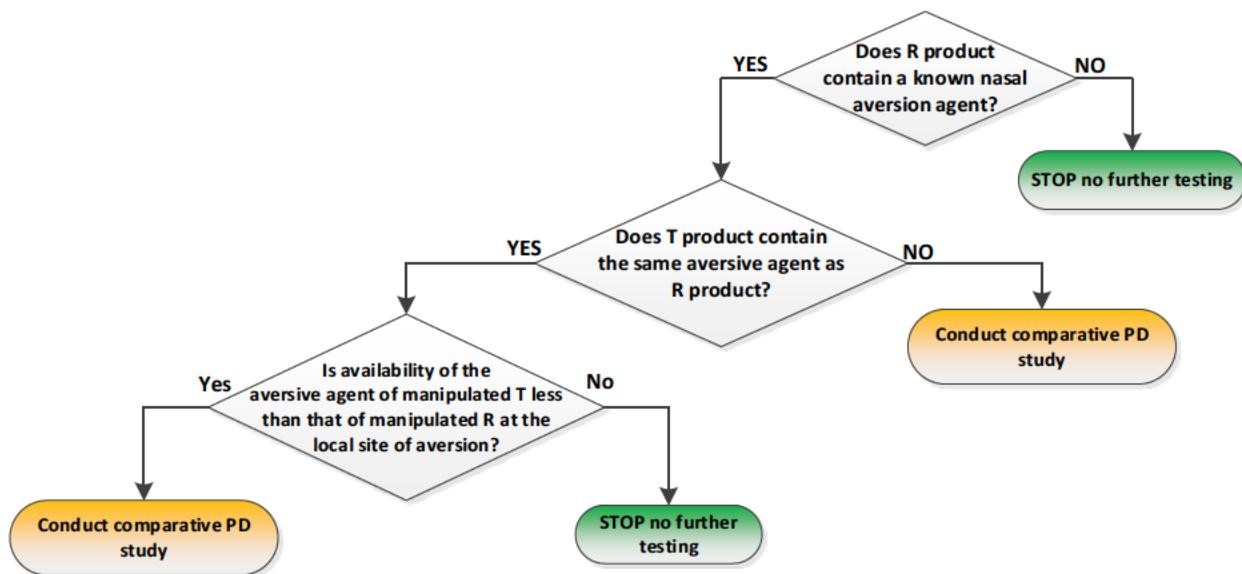


Figure 8: Evaluation of Reduced Human Abuse Potential (abuse by insufflation)

APPENDIX 5: ABUSE BY SMOKING (INHALATION ROUTE)

Abuse by smoking involves the sublimation of the active ingredient in an opioid, in its salt or free-base form, following ignition. To evaluate abuse deterrence for the inhalation route, a potential ANDA applicant should determine the amount of sublimated opioid salt or free base for intact and manipulated drug product.

The measure used to evaluate abuse by smoking is the percent of opioid sublimation calculated as: (sublimed amount/labeled strength of the R product)* 100, where the sublimated amount is the amount of drug available for smoking following ignition of the product. If R product is an agonist/antagonist combination product, the ratio of sublimation percent of agonist and antagonist should be determined.

Study conditions

Appendix 1 describes some of the ways in which solid oral opioid drug products can be physically manipulated. The potential ANDA applicant should use a household coffee grinder or other household milling appliance. The smoking test should be conducted on intact and manipulated T and R products at three different temperatures. The selected temperatures should fall within the range of 200°C to 300°C for 2 to 15 minutes.

The tier-based approach to comparative sublimation is based on using different methods to prepare the product for smoking, starting with direct sublimation of the intact and manipulated product in Tier 1, to freebasing the opioid drug substance from the intact and manipulated product prior to sublimation of the free base in Tier 2 (Table 2).

Tier 1: Sublimation of intact and manipulated products

Identify study condition. Appendix 1 describes some of the ways in which solid oral opioid drug products can be physically manipulated. If T or R product cannot be manipulated to generate particles of less than 1 mm after attempted manipulation for 5 minutes, alternate approaches such as crushing or grating after thermal pretreatment can be used to generate particles of size less than 1 mm.

Evaluate T and R products. Determine the percent of opioid sublimation of intact and manipulated R product by heating at three different temperatures between 200°C and 300°C (selected temperatures should fall within the range of 200°C to 300°C) for 2 to 15 minutes. Using the same conditions and temperatures, determine the percent of opioid sublimation of intact and manipulated T product.

Compare T and R products. Statistically compare the abuse deterrence of T and R products. If the percent of opioid sublimation of T is greater than R, then T product is less abuse deterrent than R product. If the percent of opioid sublimation of T is less than or equal to R and the opioid drug product tested is not a salt, T product is no less abuse deterrent than R and no further comparative testing of T product to R product is needed. If the percent of opioid sublimation of T is less than or equal to R and the opioid drug product is a salt, the abuse deterrence of T product should be tested further in Tier 2.

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Tier 2: Sublimation of precipitated opioid retrieved from intact and manipulated products

Identify study condition. Convert the opioid salt in intact and manipulated T and R products to precipitated free-base opioid with a household reagent (e.g., baking soda). Dry the resulting mixtures obtained from T and R products at three different temperatures (selected temperatures should fall within the range of 200°C to 300°C) for 2 to 15 minutes.

Evaluate T and R products. Determine the percent of opioid sublimation of the R product after conversion to a free base. Using the same conditions and temperatures, determine the percent of opioid sublimation of T product.

Compare T and R products. Statistically compare the abuse deterrence of T and R products. If the percent of opioid sublimation of T is greater than R, T product is less abuse deterrent than R product. If the percent of opioid sublimation of T is less than or equal to R, T product is no less abuse deterrent than R product.

Figure 9 and Table 2 illustrate the tier-based approach for evaluating the sublimation of opioid drug substance for abuse by smoking, as described above.

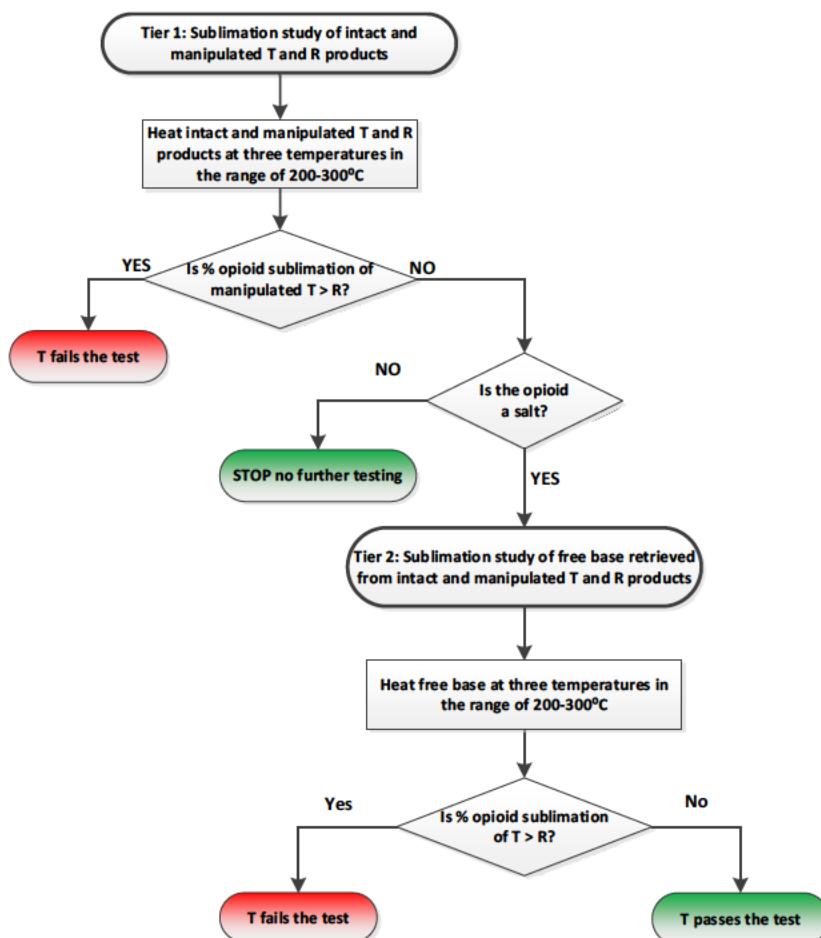


Figure 9: Decision Tree for Evaluation of Abuse Deterrence Potential (abuse by smoking)

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Table 2. Statistical Evaluation of Sublimation (abuse by smoking)

Study Condition			
Three Temperatures in the Range of 200-300°C / Duration of 2-15 minutes			
TIER 1			
Identify Study Condition	<i>Determine the % of opioid sublimation of the intact and manipulated R product.</i> <i>Using the same method, determine the % opioid sublimation of intact and manipulated T product.</i> ↓		
Evaluate the R Sublimation versus the T Sublimation	H₀: T > R versus H_a: T ≤ R If T ≤ R and % opioid drug substance is a salt <i>Conclude that % opioid sublimation of T product is less than or equal to R product; T product passes the study under Tier 1</i> CONTINUE to Tier 2 ↓	If T ≤ R and % opioid drug substance is NOT a salt <i>Conclude that % opioid sublimation of T product is less than or equal to R product; T product passes the study under Tier 1</i> STOP no further testing	If T > R <i>Conclude that % opioid sublimation of T product is greater than R product</i> STOP no further testing
TIER 2	Study Condition		
Three Temperatures in the Range of 200-300°C / Duration of 2-15 minutes			
Identify Study Condition	<i>Convert the opioid salt in intact and manipulated T and R products to free base with a household reagent. Dry the resulting mixtures obtained from the T and R products at three temperatures in the range of 200-300°C for 2-15 minutes.</i>		
Evaluate the R Sublimation versus the T Sublimation	H₀: T > R versus H_a: T ≤ R If T ≤ R <i>Conclude that % opioid sublimation of T product is less than or equal to R product; T product passes the study under Tier 2</i> STOP no further testing	If T > R <i>Conclude that % opioid sublimation of T product is greater than R product; T product fails the study under Tier 2</i> STOP no further testing	

Note: The measure used to evaluate abuse by smoking is the % of opioid sublimation, determined as follows: (sublimed amount/ labeled strength of R product)* 100, where the sublimed amount is the amount of drug available for smoking following ignition of product.

11.4. Office of Surveillance and Epidemiology Expanded Methods and Results for Postmarket Data on Stimulant Use and Nonmedical Use

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology Review (OSE)
Office of Pharmacovigilance and Epidemiology (OPE)**

**Office of Surveillance and Epidemiology Expanded Methods and Results for Postmarketing
Data on Stimulant Use and Nonmedical Use**

Date: 9/14/2020

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AR19 Capsules

Subject:
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1 GLOSSARY

AAPCC	American Association of Poison Control Centers
ADHD	Attention Deficit Hyperactivity Disorder
ADF	abuse-deterrent formulation
AE	adverse event
API	active pharmaceutical ingredient
ASI-MV	Addiction Severity Index-Multimedia Version
CII	Schedule II
CDC	Centers for Disease Control and Prevention
CHAT	Comprehensive Health Assessment for Teens
CNS	central nervous system
CV	coefficient of variation
DIM	National data on Drug-involved Mortality
ED	emergency department
ER	extended-release
FAERS	FDA Adverse Event Reporting System
FDA	Food and Drug Administration
ICD-10	International Classification of Diseases, Tenth Edition
IR	immediate-release
IV	intravenous
MTF	Monitoring the Future
NAVIPPRO	National Addictions Vigilance Intervention and Prevention Program
NDA	new drug application
NEIS-CADES	National Electronic Injury Surveillance System – Cooperative Adverse Drug Event Surveillance
NMU	nonmedical use
NPDS	National Poison Data System
NSDUH	National Survey on Drug Use and Health
NVSS-M	National Vital Statistics System-Multiple Causes of Death Database
OSE	Office of Surveillance and Epidemiology
PCC	Poison Control Center
PMR	postmarketing requirement
SNAPS	Study of Non-oral Administration of Prescription Stimulants
SUD	substance use disorder
TEDS	Treatment Episode Data Set
U.S.	United States

2 METHODS AND MATERIALS

2.1 DOCUMENTS FROM THE APPLICANT'S SUBMISSION

We reviewed the following documents included in the submission package for new drug application (NDA) 211179 from Arbor Pharmaceuticals, LLC (hereafter, Applicant), received January 15, 2020. Within these documents, we reviewed the epidemiologic data that helped support the key findings about nonmedical use (NMU) and related adverse events involving prescription stimulants based on recent postmarket data as described in **Section 9** of the United States (U.S.) Food and Drug Administration (FDA) Briefing Document: Psychopharmacologic Drugs Advisory Committee and Drug Safety and Risk Management Advisory Committee Meeting, October 8, 2020; Topic: New Drug Application 211179; Immediate-Release Amphetamine Sulfate for the Treatment of Attention Deficit Hyperactivity Disorder (hereafter, FDA Briefing Document). We assessed the internal validity as well as the external validity (generalizability) of the study findings to the U.S. population or select subpopulations; however, pre-specified study protocols for these studies were not submitted to FDA for review or approval prior to the final report submission as part of the NDA. Major features of the epidemiologic studies described in Applicant-supported study reports are presented in **Table 2**. A more detailed description of each of the Applicant-supported study reports and our analytic approach for each document is provided in **Sections 2.2.2.3 and 2.2.2.4**.

Documents included in Applicant's submission package:

- Multiple Module Information: Prescription Stimulant Nonmedical Use (NMU) Data and AR19 Manipulation Resistant and NMU Deterrent Data are Presented in This Section, prepared by Arbor Pharmaceuticals, LLC.
- Faraone SV, Hess J, Wilens T. Prevalence and Consequences of the Nonmedical Use of Amphetamine Among Persons Calling Poison Control Centers. *J. of Att. Dis.* 2019; 23(11): 1219-1228. (AR19.MA001)
- Faraone SV, Rostain AL, Montano B, Mason O, Antshel KM, Newcorn JH. Systematic Review: Nonmedical Use of Prescription Stimulants: Risk Factors, Outcomes, and Risk Reduction Strategies. *J Am Acad Child Adolesc Psychiatry.* 2020; 59(1): 100-112. (AR19.MA002)
- Inflexxion, Inc. National Addictions Vigilance Intervention and Prevention Program (NAVIPPRO[®]) Study Report Prepared for Arbor Pharmaceuticals, LLC: Analysis of Prescription Stimulants in Addiction Severity Index Multimedia Version (ASI-MV[®]) and Comprehensive Health Assessment for Teens (CHAT[®]) (AR19.MA003)
- Inflexxion, Inc. NAVIPPRO[®] Study Report Prepared for Arbor Pharmaceuticals, LLC: Analysis of Survey of Nonmedical Use of Prescription Medications among the General Population (AR19.MA004)
- Inflexxion, Inc. NAVIPPRO[®] Study Report Prepared for Arbor Pharmaceuticals, LLC: Assessing Relative Risk of Significant Medical Outcomes Associated with Prescription Amphetamine Use via Non-oral routes: Analysis of National Poison Data System (AR19.MA005)
- Inflexxion, Inc. NAVIPPRO[®] Study Report Prepared for Arbor Pharmaceuticals, LLC: Nonmedical Use of Prescription Medications in College Students (AR19.MA006)
- Inflexxion, Inc. NAVIPPRO[®] Study Report Prepared for Arbor Pharmaceuticals, LLC: Understanding Patterns of Prescription Medication Abuse and Progression to Non-oral Routes of Administration (AR19.MA008)
- University of Florida Study Report Prepared for Arbor Pharmaceuticals, LLC: Study of Non-oral Administration of Prescription Stimulants (SNAPS) (AR19.MA010)
- Pinney Associates Report Prepared for Arbor Pharmaceuticals, LLC: Public Health Rationale for AR-19 (Amphetamine Sulfate Immediate-Release Abuse Deterrent) Capsules (AR19.MA011)

- Inflexxion, Inc. NAVIPPRO® Study Report Prepared for Arbor Pharmaceuticals, LLC: Nonmedical Use of Prescription Stimulants among College Students Involved in Greek Life (Fraternity/Sorority) (AR19.MA012)
- Pinney Associates Report Prepared for Arbor Pharmaceuticals, LLC: Postmarketing Surveillance Plan for Amphetamine Sulfate Immediate Release Capsules Designed to Deter Non-oral Routes of Administration (AR19.MA014)
- W2O Group and Rho, Inc. Report Prepared for Arbor Pharmaceuticals, LLC: NOMAD Non-Oral Abuse Survey: Elucidation of Pathways to Non-Oral ADHD Prescription Stimulant Abuse (NOMAD)

2.2 FDA ANALYSES

We examined several additional data sources to describe the utilization, NMU, and related adverse outcomes (AEs) associated with prescription stimulants, with a focus on data collected in recent years. As shown in **Table 1**, currently marketed prescription stimulant drugs for oral use consist primarily of amphetamine salts and related compounds, including methylphenidate, dextroamphetamine, dexmethylphenidate, and lisdexamfetamine. Although widely recognized as an illicitly manufactured street drug, methamphetamine is also a regulated Schedule II (CII) oral stimulant product. Cocaine is another widely recognized stimulant street drug that is approved as a CII topical solution for local anesthesia of mucous membranes. We excluded non-oral formulations of stimulants from the table such as methylphenidate transdermal patches for treatment of attention deficit hyperactivity disorder (ADHD). Whenever possible, we provided the analogous data for prescription opioid analgesics to provide context for prescription stimulant NMU, given that opioid analgesics are the only drug class with some products currently labeled as having properties expected to deter abuse via certain routes. Where available, information on illicit stimulants was also included, for context. The data sources collected information from various populations, including the general population, subgroups of the general population (e.g., college students, people with ADHD), enriched populations (e.g., people being assessed for substance use disorder (SUD) treatment, people who use stimulants via non-oral routes), people filling prescriptions in the outpatient retail setting, and people seeking advice or medical treatment for adverse effects of NMU. We present major features of drug utilization data sources in **Section 2.2.1**, and major features of relevant epidemiologic data sources as well as detailed descriptions of all included data sources and our analytic approach in **Section 2.2.2** and **Section 4**.

Table 1. FDA approval dates of marketed oral CII stimulant products

Molecule	Brand Name Product	Applicant	NDA/ANDA	FDA Approval Date
Amphetamine	Adzenys ER	Neos Theraps Inc	204325	9/15/2017
	Adzenys XR-ODT	Neos Theraps Inc	204326	1/27/2016
	Dyanavel XR	Tris Pharma Inc	208147	10/19/2015
	Evekeo	Arbor Pharms LLC	200166	8/9/2012
	Evekeo ODT	Arbor Pharms LLC	209905	1/30/2019
Dextroamphetamine	Dexedrine	Impax Labs Inc	017078	8/2/1976
Lisdexamfetamine	Vyvanse	Shire	021977 208510	2/23/2007 1/28/2017
Methamphetamine	Desoxyn	Recordati Rare	005378	12/31/1943
Mixed Amphetamine Salts	Adderall XR	Shire	021303	10/11/2001
	Mydayis	Shire Dev LLC	022063	6/20/2017
Dexmethylphenidate	Focalin	Novartis	021278	11/3/2001
	Focalin XR	Novartis	021802	5/26/2005
Methylphenidate	Adhansia XR	Purdue Pharma LP	212038	2/27/2019
	Aptensio XR	Rhodes Pharms	205831	4/17/2015

	Cotempla XR-ODT	Neos Theraps Inc	205489	6/19/2017
	Concerta	Janssen	021121	8/1/2000
	Daytrana*	Noven Pharms Inc	021514	4/6/2006
	Jornay PM	Ironshore Pharms	209311	8/8/2018
	Metadata CD	UCB Inc	021259	4/3/2001
	Metadata ER	UCB Inc.	089601	6/1/1988
	Methylin	Mallinckrodt	021419	12/19/2002
	Methylin ER	Mallinckrodt	075629	5/9/2000
	QuilliChew ER	Pfizer	207960	12/4/2015
	Quillivant XR	NextWave	202100	9/27/2012
	Ritalin	Novartis	010187	12/15/1955
	Ritalin LA	Novartis	021284	6/5/2002
	Ritalin SR	Novartis	018029	3/30/1982

* Transdermal system

ANDA, abbreviated new drug application; CD, controlled-delivery; CII, Schedule II; ER, extended-release; FDA, Food and Drug Administration; LA, long-acting; NDA, new drug application; ODT, oral disintegrating tablet; PM, bedtime dosing; XR, extended-release.
Source: Drugs@FDA: FDA-Approved Drugs. Available at: <https://www.accessdata.fda.gov/scripts/cder/daf/>. (accessed June 5, 2020).

2.2.1 Drug Utilization Methods and Materials

We used proprietary drug utilization databases available to the Agency to conduct these analyses. Detailed descriptions of the databases are included in **Section 4.1**.

2.2.1.1 Data Sources Used

We used IQVIA, National Sales Perspectives™ database to determine the settings of care where CII stimulant products were sold from manufacturers to the various channels of distribution in the United States for 2019.

We used IQVIA, National Prescription Audit™ database to determine the estimated number of prescriptions dispensed for CII stimulants by immediate or extended-release formulation and by drug from U.S. outpatient retail pharmacies from the second quarter of 2014 to the fourth quarter of 2019. We also used this database to determine the estimated number of prescriptions dispensed for CII stimulants, stratified by patient age (<20 years, 20-64 years, 65+ years) from January 2008 through December 2019.

We used IQVIA, Total Patient Tracker™ database to determine the estimated number of unique patients who received dispensed prescriptions for CII stimulants, stratified by patient age (<6 years, 6-12 years, 13-19 years, 20-39 years, 40-59 years, and 60+ years) from U.S. outpatient retail pharmacies from January 2008 through December 2019.

We used the Syneos Treatment Answers™ database to determine the top diagnoses associated with the use of CII stimulants as reported by office-based physicians, stratified by patient age (<20 years, 20 to 64 years, and 65+ years) from January 2011 through December 2012 and January 2018 through December 2019.

2.2.2 Methods and Materials for Epidemiologic Review of NMU

2.2.2.1 Purpose and Scope of Epidemiologic Review of NMU

The purpose of this epidemiologic review of NMU was to provide a population perspective on the prevalence, patterns (including route of administration), correlates (e.g., reasons, sources, polysubstance use), and trends of CII prescription stimulant NMU, as well as morbidity and mortality associated with these products. We examined multiple data sources to describe the NMU and related adverse outcomes associated with CII prescription stimulants, as well as illicit stimulants when possible. We also included results of analyses from Applicant-submitted reports that helped to address the key findings related to

Section 9 of the FDA Briefing Document. Applicant-submitted reports came from studies conducted by various academic researchers, internet panel survey companies, and data vendors that were funded by the Applicant. We refer to those studies by the report numbers AR19.MAXXX, where XXX is the report number.

We also provided patterns of prescription opioid analgesic NMU, where possible, for context since there are several products currently labeled as having properties expected to deter abuse via certain routes of administration including chewing, nasal, and injection. The postmarketing experience for opioid analgesics may provide insights into the potential public health risks and benefits and relevant postmarket questions for this prescription abuse-deterrent formulation (ADF) stimulant product.

The data sources collected information from various populations, including the general population, college students, enriched populations (e.g., people with non-oral stimulant use), people seeking advice or medical treatment for adverse effects of NMU, and individuals entering or being assessed for SUD treatment. For most analyses, CII prescription stimulants were treated as a class or presented at the level of the active pharmaceutical ingredient (API). **Table 2** provides a roadmap of the analyses conducted by FDA or included in Applicant-submitted reports by describing the major features of each data source, the subsection of the results in which we used the data, and the definition of NMU from the data source. We did not include all analyses from the Applicant-submitted reports when we had conducted a more updated or relevant analysis of the same data source, where we had methodological concerns, and where the results did not address our key questions in **Section 9.1** of the FDA Briefing Document. A more detailed description of each data source and our analytic approach is provided in the sections below.

Table 2. Overview of epidemiologic data sources and studies on NMU of prescription stimulants and other drugs that were conducted by the FDA or from Applicant reports

<i>FDA Data</i>			
Data Source	Source/Population	Use of Data	Definition of NMU
NSDUH, 2015–2018	Nationally representative household survey General U.S. population, persons aged 12 years or older	<ul style="list-style-type: none"> • Scale of NMU • Polysubstance use • Reasons for NMU • Source for NMU • Trajectory for NMU 	Misuse: Use in any way not directed by a doctor, including use without a prescription of one's own; use in greater amounts, more often, or longer than told to take a drug; or use in any other way not directed by a doctor.
MTF, 2013–2019	School-based survey General U.S. population; persons in 8 th , 10 th , 12 th grades	<ul style="list-style-type: none"> • Scale of NMU 	Use: On your own—that is, without a doctor telling you to take them.
AAPCC, NPDS, 2001–2018	NPDS cases from calls to U.S. Poison Control Centers People seeking advice regarding drug exposures	<ul style="list-style-type: none"> • Scale of NMU • Routes of administration • Polysubstance use • Morbidity of NMU 	NMU: Includes: Intentional – Misuse: “An exposure resulting from the intentional improper or incorrect use of a substance for reasons other than the pursuit of a psychotropic effect.” Intentional – Abuse: “An exposure resulting from the intentional improper or incorrect use of a substance where the victim was likely attempting to gain a high, euphoric effect, or some other psychotropic effect.” This includes

			recreational use of a substance for any effect.
NEISS-CADES, 2016–2018	Nationally representative sample of emergency department visits for adverse effects of pharmaceutical products	<ul style="list-style-type: none"> • Scale of NMU • Polysubstance use • Morbidity of NMU 	<p>NMU: Includes:</p> <ul style="list-style-type: none"> • Documented abuse: Clinician diagnosis of abuse or documented recreational use. • Therapeutic misuse: Documented therapeutic intent, but the pharmaceutical was not used as directed. • Overdoses without documentation of therapeutic intent, self-harm, abuse, or misuse.
NEISS-CADES – Published Analysis by Geller et al., 2019,* January 2016–December 2016	Nationally representative sample of ED visits for adverse effects of pharmaceutical products	<ul style="list-style-type: none"> • Scale of NMU • Polysubstance use • Morbidity of NMU 	<p>NMU: Includes:</p> <ul style="list-style-type: none"> • Documented abuse: Clinician diagnosis of abuse or documented recreational use. • Therapeutic misuse: Documented therapeutic intent, but the pharmaceutical was not used as directed. • Overdoses without documentation of therapeutic intent, self-harm, abuse, or misuse.
TEDS, 2007–2017	Nonrepresentative, dynamic population sample of individuals admitted for abuse of alcohol and/or drugs in facilities that report to state administrative data systems, aged 12 years and older	<ul style="list-style-type: none"> • Scale of NMU 	<p>Primary Substance: The substance that led to the treatment admissions for substance use.</p>
NAVIPPRO®, ASI-MV®, 2013–2019	Nonrepresentative, dynamic population sample of individuals being assessed or seeking treatment for SUD, aged 17 years and older	<ul style="list-style-type: none"> • Scale of NMU** • Routes of administration** 	<p>Abuse/NMU: Use of the specified prescription product in a way not prescribed by your doctor, via alternative routes of administration, and/or obtained from sources not associated with a prescriber.</p>
NVSS-MCD, 1999–2018	Coded data on drug classes involved in U.S. overdose deaths	<ul style="list-style-type: none"> • Mortality of NMU 	<p>Overdose deaths: Identified using codes from the International Classification of Diseases, Tenth Revision.</p> <ul style="list-style-type: none"> • Psychostimulants with abuse potential (T43.6) • Heroin (T40.1) • Natural and semisynthetic opioids (T40.2) • Methadone (T40.3) • Synthetic opioids excluding methadone (T40.4)
DIM, 2010–2014	Drugs mentioned in literal text of U.S.	<ul style="list-style-type: none"> • Mortality of NMU 	<p>Drugs of interest</p> <ul style="list-style-type: none"> • Amphetamine

	death certificates as contributing to the death		<ul style="list-style-type: none"> • Dexmethylphenidate • Dextroamphetamine • Lisdexamfetamine • Methamphetamine • Methylphenidate
<i>Applicant-Submitted Data</i>			
Data Source	Source/Population	Use of Data	Definition of NMU
AR19.MA001 – A Report of NPDS Data, 2012–2016***	<p>NPDS cases from calls to U.S. Poison Control Centers</p> <p>People seeking advice regarding drug exposures involving NMU of prescription amphetamine, persons aged >12 years</p>	Results not included in review	<p>NMU: Intentional use of a prescription stimulant without a prescription, or in a way other than prescribed; it encompasses both abuse and misuse.</p>
AR19.MA003 – A Report of Adult ASI-MV® Data, 2010–2017	Nonrepresentative, dynamic population sample of individuals being assessed or seeking treatment for SUD, aged 18 years or older	<ul style="list-style-type: none"> • Scale of NMU • Routes of administration • Source for NMU 	<p>NMU: Determined by an algorithm from responses given during a computer-administered interview. The questions asked were whether the medication was obtained from their own prescription; the medication had been used via an alternate route of administration (i.e., not as prescribed); used in a way not prescribed by the doctor, but for the way it makes one feel and not for the treatment of the drug's indicated disease.</p>
AR19.MA003 – A Report of Adolescent CHAT® Data, 2010–2017	Nonrepresentative, dynamic population sample of adolescents seeking treatment for substance abuse, aged 18 years or younger	<ul style="list-style-type: none"> • Scale of NMU • Routes of administration • Source for NMU 	<p>NMU: Use not as prescribed or to get high.</p>
AR19.MA004 – An Online Survey of the General U.S. Population Conducted by the Internet Panel Company YouGov, July–September 2018	<p>Anonymous internet survey</p> <p>General U.S. population, persons aged 18 to 49 years</p>	<ul style="list-style-type: none"> • Scale of NMU • ADHD and NMU • Routes of administration • Polysubstance use • Reasons for NMU • Risk factors for NMU • Source for NMU • Trajectory for NMU 	<p>NMU: Use for any reason, even once, without your own prescription; Use in ways other than prescribed (such as taking more than prescribed, more often than prescribed, or for any other reason/way than prescribed; Use for the feeling or experience the medication caused (such as feeling of being high, enhancement of other drugs, prevention or treatment of withdrawal symptoms or other feelings).</p>

AR19.MA005 – A Report of NPDS Data, 2012–2016	<p>NPDS cases from calls to U.S. Poison Control Centers</p> <p>People seeking advice regarding drug exposures involving NMU of prescription amphetamine, persons aged >12 years</p>	Results not included in review	<p>NMU: Includes:</p> <p>Intentional – Abuse: An exposure resulting from the intentional improper or incorrect use where the patient was likely attempting to gain a high, euphoric effect, or some other psychotropic effect, including recreational use of a substance for any effect.</p> <p>Intentional – Misuse: An exposure resulting from the intentional improper or incorrect use for reasons other than the pursuit of a psychotropic effect.</p> <p>Intentional – Unknown: An exposure that is determined to be intentional, but the specific motive is unknown.</p>
AR19.MA006 – An Online Survey of the General U.S. College-Aged Population Conducted by the Internet Panel Company YouGov, July–November 2018	<p>Internet survey</p> <p>College students aged 18 to 26 years</p>	Results not included in review	<i>See AR19.MA004 definition.</i>
AR19.MA008 – An Online Survey of Adult Reddit Users with a History of Nonoral Prescription Stimulant Use, February–September 2019	<p>Anonymous internet survey</p> <p>Persons aged 18 years or older with a history of NMU of prescription stimulants, via at least one nonoral route of administration</p>	<ul style="list-style-type: none"> • Scale of NMU • Routes of administration • Polysubstance use • Trajectory for NMU 	<i>See AR19.MA004 definition.</i>
AR19.MA010 – An Anonymous In-Person Interviewer-Facilitated Survey of General Population Youth, Conducted by the Substance Abuse Training Center in Public Health at the University of Florida, August–November 2018	<p>Anonymous in-person youth survey</p> <p>General population youth; persons aged 10 to 17 years at public venues (e.g., malls, arcades) from six cities in three U.S. states</p>	<ul style="list-style-type: none"> • Routes of administration • Reasons for NMU • Source for NMU 	<p>NMU (main definition): Taking the stimulant product nonorally, taking the stimulant product from someone else, or taking the stimulant product more than prescribed in the past 30 days or in your lifetime but not in the past 30 days.</p>
AR19.MA011 – A Report of NSDUH Data Conducted by Pinney Associates, 2010–2018	<p>Nationally representative household survey</p> <p>General U.S. population, persons</p>	<ul style="list-style-type: none"> • Scale of NMU 	<p>Misuse: Use in any way not directed by a doctor, including use without a prescription of one's own; use in greater amounts, more often, or longer than told to take a drug; or use in any other way not directed by a doctor.</p>

	aged 12 years or older		
AR19.MA011 – A Report of MTF Data Conducted by Pinney Associates, 1980–2018	School-based survey General U.S. population; persons in 8 th , 10 th , 12 th grades	• College enrollment and NMU	Use: On your own—that is, without a doctor telling you to take them.
AR19.MA012 – An Online Survey of the General U.S. College-Aged Population Conducted by the Internet Panel Company YouGov, July–September 2018 and February–September 2019	Anonymous internet survey General U.S. population, persons aged 18 to 26 years	• Scale of NMU • College enrollment and NMU • Routes of administration • Polysubstance use • Reasons for NMU • Source for NMU	<i>See AR19.MA004 definition.</i>
NOMAD – An Online Survey of Adults with a History of Non-oral Prescription Stimulant Use Conducted by the research Organization W2O/Marketeching, August–September 2018	Anonymous internet survey Persons aged 18 years or older that had used an ADHD prescription stimulant, via a non-oral route of administration	• ADHD and NMU • Routes of administration • Trajectory for NMU	Abuse: taken any prescription ADHD stimulant, even once, for any reason other than treating ADHD symptoms, such as staying awake, getting high, increasing energy, enhancing performance, etc.

ADHD, Attention Deficit Hyperactivity Disorder; ED, emergency department; SUD, Substance Use Disorder; U.S., United States; AAPCC, American Association of Poison Control Centers; ASI-MV[®], Addiction Severity Index-Multimedia Version; CHAT[®], Comprehensive Health Assessment for Teens; DIM, National Data on Drug-Involved Mortality; FDA, U.S. Food and Drug Administration; MTF, Monitoring the Future; NAVIPPRO[®], National Addictions Vigilance Intervention and Prevention Program; NEISS-CADES, National Electronic Injury Surveillance System–Cooperative Adverse Drug Event Surveillance; NFLIS, National Forensic Laboratory Information System; NMU, nonmedical use; NPDS, National Poison Data System; NSDUH, National Survey on Drug Use and Health; NVSS-MCD, National Vital Statistics System–Multiple Cause of Death Database; TEDS, Treatment Episode Data Set.

Applicant Report Titles: AR19.MA001: See Faraone et al., 2019 reference, below. AR19.MA003: Analysis of Prescription Stimulants in ASI-MV[®] and CHAT[®]; AR19.MA004: Analysis of Survey of Nonmedical Use of Prescription Medications among the General Population; AR19.MA005: Assessing Relative Risk of Significant Medical Outcomes Associated with Prescription Amphetamine Use via Non-Oral Routes: Analysis of National Poison Data System; AR19.MA006: Nonmedical Use of Prescription Medications in College Students; AR19.MA008: Understanding Patterns of Prescription Medication Abuse and Progression to Non-oral Routes of Administration; AR19.MA010: The Study of Non-oral Administration of Prescription Stimulants (SNAPS); AR19.MA011: Public Health Rationale for AR-19 (Amphetamine Sulfate Immediate Release Abuse Deterrent) Capsules; AR19.MA012: Nonmedical Use of Prescription Medications in College Students Involved in Greek Life (Fraternity or Sorority); NOMAD, The NOMAD Non-Oral Abuse Survey: Elucidation of Pathways to Non-Oral ADHD Prescription Stimulants Abuse.

Note: “*” This includes results a published analysis of 2016 NEISS-CADES data: Geller AI, Dowell D, Lovegrove MC, McAninch JK, Goring SK, Rose KO, Weidle NJ, and Budnitz DS. U.S. Emergency Department Visits Resulting From Nonmedical Use of Pharmaceuticals, 2016. *Am J Prev Med.* 2019; 56 (5): 639-647.

Note: “**” indicates that the analysis only included prescription opioid analgesics.

Note: “***” Faraone SV, Jess J, and Wilens T. Prevalence and Consequences of the Nonmedical Use of Amphetamine Among Persons Calling Poison Control Centers. *J. of Att. Dis.* 2019; 23 (11): 1219-1228.

2.2.2.2 Classification of Prescription and Illicit Stimulants

We focused our epidemiologic review of NMU patterns on CII stimulant medications indicated primarily for treatment of ADHD, as described in **Table 1**, shown above. Wherever possible, we excluded data on other stimulants, such as caffeine, ephedrine, or products indicated solely for weight loss (e.g., phentermine). The exact drugs included in the prescription stimulant category depended on the data source being used. Some studies referred to “prescription stimulants,” “ADHD medications,” “prescription ADHD stimulants,” etc. Wherever available, we noted which drugs were included in the

category. When describing a specific study, we generally used the term “*nonmedical use*,” which combines the concepts of misuse and abuse under one term. As previously mentioned, we provide the original definitions from each data source that we considered under the term “NMU” in **Table 2**, above.

Some CII prescription and regulated pharmaceutical stimulant APIs are also widely manufactured illicitly, such as methamphetamine and cocaine. The sales volume of prescription methamphetamine is extremely low. We generally assumed that when the term “methamphetamine” was used with respect to overdose or NMU, it primarily referred to illicit methamphetamine, and therefore was not included when referring to CII prescription stimulants. However, we were able to distinguish between prescription methamphetamine and illicit methamphetamine products in National Poison Data System (NPDS), and therefore we included prescription methamphetamine exposure cases with other CII prescription stimulant cases in that data source. Regulated pharmaceutical cocaine is only indicated for local anesthesia during diagnostic or surgical procedures, so we assumed that when the term “cocaine” was used, it primarily referred to illicit cocaine and therefore was not included when referring to CII prescription stimulants.

2.2.2.3 Applicant-Submitted Epidemiologic Studies and Data Analyses

Some Applicant-submitted studies described in **Table 2** are not included in **Section 2.2.2.3** as we did not include all studies or analyses when there was a more updated or relevant analysis of the same data source, where we had methodological concerns, and where the results did not address our key questions. The “Use of Data” column in **Table 2** notes whether and how we used the data from the Applicant reports.

2.2.2.3.1 Analysis of Prescription Stimulants in ASI-MV® and CHAT® (AR19.MA003)

Data Source: This study included two separate analyses of sentinel programs within NAVIPPRO®: ASI-MV® and CHAT®. The first analysis included 512,972 ASI-MV® assessments of adults 18 years or older being assessed for substance abuse problems or treatment planning within a network of public and private facilities throughout the United States (48 total states contributed to this analysis). The second analysis included 20,305 CHAT® respondents 18 years or younger that were also being assessed for substance abuse problems or treatment planning with a network of public and private facilities throughout the United States (36 total states contributed to this analysis). Both analyses included self-reported information, collected between January 1, 2010 and September 30, 2017, on NMU drug patterns including prescription stimulants, other prescription medications (e.g., opioid analgesics), and illicit drug use. The final AR19.MA003 report provided descriptive statistics of overall and yearly NMU of prescription stimulants among adults and adolescents, including information on routes of administration, and the source of prescription medications.

Definitions:

- **NMU (ASI-MV®):** Determined using an algorithm that utilizes responses given during a computer-administered interview. The questions asked were whether the medication was obtained from their own prescription; used via an alternate route of administration (i.e., not as prescribed); used in a way not prescribed by the doctor, but for the way it makes one feel and not for the treatment of the drug’s indicated disease.
- **NMU (CHAT®):** Defined as use not as prescribed or use to get high.
- **Any Oral Route:** Defined as swallowing whole, chewing prior to swallowing, dissolving then swallowing, or drinking.
- **Any Non-Oral Route:** Defined as snorting, smoking, injecting, or other.

Search Parameters and Data Analysis: We abstracted relevant results from detailed data tables provided in the final AR19.MA003 report. We abstracted data pertaining to overall NMU of prescription stimulants, routes of administration, and the source of prescriptions. We reported data on individually defined non-oral routes (i.e., snorting, smoking, injecting). The composition of the ‘other’ non-oral route

category was not defined and comprised <5% of the total ASI-MV® and CHAT® assessments for NMU of any prescription stimulant. Unless otherwise noted, we reported values in terms of percent for the overall population. Yearly trends were reported as rates per 100 assessments and per 100,000 prescription dispensed for selected prescriptions stimulants.

2.2.2.3.2 Nonmedical Use of Prescription Medications among the General Population (AR19.MA004)

Data Source: Conducted by the survey panel company YouGov, AR19.MA004 was an anonymous web-based survey of U.S. adults between the ages of 18 and 49 years. The final study population included 12,000 respondents who were recruited via email between July 27, 2018 and September 2, 2018. The survey employed a stratified sampling scheme, based on the 2016 American Community Survey,¹ to reflect the U.S. adult population in terms of sex, age, race, and education. Data were collected on a range of topics including demographics, medical conditions, history of substance abuse (prescription and illicit drugs), NMU of prescription drugs, routes of administration, sources of drugs, motivations for using drugs, frequency of use of drugs, and negative consequences of using prescriptions drugs. The main goals of the study were to (1) evaluate the overall NMU of prescription stimulant medications in the general population and (2) characterize the motives, methods, and factors related to NMU of prescription stimulants in the general population. The final AR19.MA004 report provided results on the prevalence of NMU of prescription medications, including stimulants, and multivariable logistic regression analyses of risk factors associated with lifetime NMU of prescription stimulants.

Definitions:

- **NMU:** Defined as use for any reason, even once, without your own prescription; Use in ways other than prescribed (such as taking more than prescribed, more often than prescribed, or for any other reason/way than prescribed; Use for the feeling or experience the medication caused (such as feeling of being high, enhancement of other drugs, prevention or treatment of withdrawal symptoms or other feelings).
- **Any Oral Route:** Defined as swallowing whole, chewing in mouth then swallowing, or dissolving in liquid then swallowing.
- **Any Non-Oral Route:** Defined as snorting, smoking, or injecting.

Search Parameters and Data Analysis: Relevant results were abstracted from detailed data tables provided in the final AR19.MA004 report, which included data pertaining to overall NMU of prescription stimulants, routes of administration, determinants and risk factors for NMU overall and for non-oral NMU (compared to oral NMU), reasons for NMU, source of prescription stimulants for NMU, polysubstance drug use, and drug use trajectories. For selected comparisons analogous results were included for prescription opioid analgesic NMU. Unless otherwise noted, data were reported as the percentage of the overall population or defined subpopulations.

2.2.2.3.3 Understanding Patterns of Prescription Medication Abuse and Progression to Non-Oral Routes of Administration (AR19.MA008)

Data Source: An additional anonymous web-based survey conducted by YouGov of English-speaking U.S. adults 18 years or older, AR19.MA008 focused on adults with NMU of a prescription stimulant by a non-oral route of administration. Participants were invited to take the survey from advertisements posted on the online forum Reddit between February and September 2019. The final study population included 225 participants. The survey collected a range of data pertaining to demographics, medical history, NMU of prescription medications, and history of illicit substance use. The main goals of the study were to (1)

¹ American Community Survey. Available at: <https://www.census.gov/programs-surveys/acs>. (accessed August 25, 2020).

evaluate pathways surrounding NMU of prescription stimulants by a non-oral route of administration, (2) examine the role of illicit drug use in these pathways, and (3) evaluate the temporal trends of use of other substances and routes of administration related to NMU of prescription stimulants. The final AR19.MA008 report provided descriptive statistics for the overall study population and stratified by non-oral routes of administration for lifetime NMU of prescription stimulants, opioids, and other subgroups of interest.

Definitions:

- **NMU:** Defined as use for any reason, even once, without your own prescription; Use in ways other than prescribed (such as taking more than prescribed, more often than prescribed, or for any other reason/way than prescribed); Use for the feeling or experience the medication caused (such as feeling of being high, enhancement of other drugs, prevention or treatment of withdrawal symptoms or other feelings).
- **Any Oral Route:** Defined as swallowing whole, cutting or breaking into smaller pieces then swallowing, chewing in mouth then swallowing, or dissolving in liquid then swallowing.
- **Any Non-Oral Route:** Defined as snorting, smoking, or injecting.

Search Parameters and Data Analysis: Relevant results were abstracted from detailed data tables provided in the final AR19.MA008 report, which included data pertaining to overall NMU of prescription stimulants, routes of administration, polysubstance drug use, and drug use trajectories. Unless otherwise noted, data were reported as the percent of the overall population or defined subpopulations.

2.2.2.3.4 The Study of Non-Oral Administration of Prescription Stimulants (AR19.MA010)

Data Source: The Study of Non-Oral Administration of Prescription Stimulants (SNAPS) was an anonymous in-person interviewer-facilitated cross-sectional survey of adolescents ages 10 to 17 years recruited from public venues (e.g., malls, arcades) from six cities in three U.S. states (Florida, Texas, and California) from August through November 2018. The study was conducted by the Substance Abuse Training Center in Public Health at the University of Florida. There were 1,777 surveys included. Investigators excluded surveys where the interviewee cognition was poor; most questions were left blank; and youth were determined to be randomly selecting answers without reading the question, as determined by the lead raters at each site. The study report described an aim to enrich the sample with adolescents at highest risk for non-oral stimulant use as well as to ensure representation of various ethnicities, LGBTQ populations, and both urban and rural settings. However, the sampling methods to enrich the sample and improve representativeness of demographics and urban/rural settings were unclear. The investigators applied participation restrictions on groups of friends to avoid weighting the results with their shared experiences. Surveys collected information on sociodemographic factors; health; gambling; medical and nonmedical substance use, including prescription stimulants; route of administration; reasons for substance use; substance use trajectories; and perceptions of friends' substance use.

The main goals of the study were to (1) assess the prevalence and predictors of routes of administration of prescription stimulants among adolescents, (2) identify trajectories from oral to non-oral use of prescription stimulants, and (3) assess sources and motivations for various routes of NMU and diversion. The final AR19.MA010 report provided results on the prevalence of use and NMU of prescription stimulants in the past 30 days and in their lifetime, including routes of administration, age at first use, reasons for use, diversion, and polysubstance use.

Definitions:

- **NMU:** Taking the stimulant product non-orally, taking the stimulant product from someone else, or taking the stimulant product more than prescribed in the past 30 days or in your lifetime (but not in the past 30 days).
- **Any Oral Route:** Use by mouth.

- **Any Non-oral Route:** Defined as snorted/sniffed, smoked, or injected.

Search Parameters and Data Analysis: Relevant results were abstracted from detailed data tables provided in the final AR19.MA010 report, which included data pertaining to routes of non-oral administration, reasons for NMU, and the source of prescriptions for NMU. Since the study report described an attempt to enrich the sample with adolescents at highest risk for non-oral stimulant use and non-oral use was one of the criteria to define NMU, estimates from this report were not used on the prevalence of NMU or oral vs non-oral stimulant use. However, information was abstracted about oral and non-oral use patterns among youth who reported non-oral use.

2.2.2.3.5 Nonmedical Use of Prescription Medications in College Students Involved in Greek Life (AR19.MA012)

Data Source: This study is two separate sub-analyses of data collected from the previously described YouGov web-based surveys, AR19.MA004 and AR19.MA006. The first analysis included 3,011 respondents from AR19.MA004 that were between the ages of 18 and 26 years. Of those, 1,356 respondents were enrolled in college, with 157 also being involved in Greek life (i.e., participated in a fraternity/sorority). The main goal of this sub-analysis was to describe the prevalence of prescription stimulant use, patterns, and associated behaviors of college students involved in Greek life compared to individuals of the same age that were enrolled in college but not involved in Greek life and those not enrolled in college. The second sub-analysis included a total of 583 respondents (N = 97 from AR19.MA004; N = 486 from AR19.MA006) currently enrolled in college with a history of NMU of prescription stimulants. The main goal of this sub-analysis was to assess demographic and drug use patterns of college students with a history of NMU of prescription stimulants and compare those that were involved in Greek life to those that were not. The final AR19.MA012 report provided descriptive statistics of the overall study population and stratified by college status and Greek life involvement, for NMU of prescription stimulants, opioids, and other subgroups of interest.

Definitions:

- **NMU:** Defined as use for any reason, even once, without your own prescription; Use in ways other than prescribed (such as taking more than prescribed, more often than prescribed, or for any other reason/way than prescribed; Use for the feeling or experience the medication caused (such as feeling of being high, enhancement of other drugs, prevention or treatment of withdrawal symptoms or other feelings).
- **Any Oral Route:** Defined as swallowing whole, chewing in mouth then swallowing, or dissolving in liquid then swallowing.
- **Any Non-Oral Route:** Defined as snorting, smoking, or injecting.
- **Greek life:** Defined as involvement in a fraternity or sorority.

Search Parameters and Data Analysis: Relevant results for the first sub-analysis were abstracted from detailed data tables provided in the final AR19.MA012 report, which included data pertaining to overall NMU of prescription stimulants, routes of administration, reasons for NMU, source of prescription, polysubstance drug use, and drug use trajectories. Unless otherwise noted, data were reported in terms of percent for the overall population or stratified by college enrollment status (i.e., non-college, college non-Greek, college Greek). Data were not abstracted from the second sub-analysis due to methodological concerns related to AR19.MA006.

2.2.2.3.6 The NOMAD Non-Oral Abuse Survey: Elucidation of Pathways to Non-Oral ADHD Prescription Stimulant Abuse (NOMAD)

Data Source: A cross-sectional anonymous web-based survey, NOMAD was developed, conducted, and implemented by the research organization W2O/Marketeching in collaboration with the Applicant and Rho, Inc. The study included a total of 1,005 adults aged 18 years or older that reported non-oral NMU of

an ADHD prescription stimulant enrolled between August 27, 2018 and September 19, 2018. The final study population included 575 respondents diagnosed with ADHD. The goals of the NOMAD study were to (1) identify and describe individuals who have nonmedically used an ADHD prescription stimulant via a non-oral route; (2) map and describe the progression, pathways, and outcomes surrounding the non-oral ADHD prescription stimulant NMU event; and (3) evaluate the population that may benefit from a non-oral ADF prescription stimulant.

Definitions:

- **Abuse:** Use of any prescription ADHD stimulant, even once, for any reason other than treating ADHD symptoms, such as staying awake, getting high, increasing energy, enhancing performance, etc.
 - The above definition of *abuse* is from the questionnaire used to screen participants, which differed and was more descriptive than the definition of *abuse* provided in the NOMAD report (i.e., intentional non-therapeutic insufflation, injection, inhalation or smoking of a stimulant to achieve a desirable psychological or physiological effect).
- **Non-Oral:** Defined as intranasal (snorting), intravenous (injecting), or inhalation (smoking).

Search Parameters and Data Analysis: Detailed data tables provided in the final NOMAD report included descriptive statistics related to the study demographics and specific survey responses for the overall study population and stratified by ADHD diagnosis. Data were abstracted pertaining to NMU of prescription ADHD stimulants, routes of administration, and drug use trajectories. Data were reported in terms of percent for the overall NOMAD population and stratified by ADHD diagnosis.

2.2.2.4 Other Applicant-Submitted Reports

2.2.2.4.1 Prescription Stimulant Nonmedical Use Data, Role of AR19 in Deterring Non-oral Prescription Stimulant Nonmedical Use Data, Postmarketing Surveillance Plan, and Proposed Postmarketing Studies (1.11.4 Multiple Module Information)

This report provided an overall summary and rationale for the development and proposed public health benefits of AR19, an immediate-release (IR) ADF amphetamine sulfate product, as well as proposed postmarketing studies. The majority of this report focused on NMU of prescription stimulants based on requests made by FDA at a pre-NDA meeting in August 2018. The report included many analyses from a variety of data sources on the prevalence of NMU of prescription stimulants by population and route of administration as well as risk factors, predictors, motives, types of stimulants used, diversion, polysubstance use, associated adverse medical outcomes, and trajectories for NMU of prescription stimulants and development of SUD. This report outlined the potential role of AR19 in deterring non-oral NMU of prescription stimulants and how that deterrence would fill an unmet need. This report also presented the Applicant's postmarketing surveillance plan and prescriber education plan (not discussed in this review), and proposed postmarketing studies. This report was used to understand the Applicant's positions on the proposed public health benefits of AR19.

2.2.2.4.2 Public Health Rationale for AR-19 (Amphetamine Sulfate Immediate-Release Abuse Deterrent) Capsules (AR19.MA011)

This report outlined an argument for the public health benefits of a prescription stimulant product with properties that deter non-oral NMU. To support their position, the report incorporated results from Applicant studies, literature, and publicly available federal data sources on the prevalence, route of administration, motivations, diversion, and adverse medical outcomes of prescription stimulant NMU. The report also discusses the relationship between prescription stimulant NMU and use of illicit substances and attempted to assess the potential for substitution of illicit substances after marketing of a prescription stimulant with properties designed to deter abuse. Selected data tables and figures were

abstracted from this report, as described in **Table 2**. This report was also used for additional commentary on potential public health risks and benefits of AR19 or other ADF stimulants.

2.2.2.4.3 Postmarketing Surveillance Plan for Amphetamine Sulfate Immediate-Release Capsules Designed to Deter Non-Oral Routes of Administration (AR19.MA014)

This report outlined some proposed postmarketing surveillance goals to:

1. monitor, detect and evaluate potential signals of misuse, abuse, overdose and diversion of AR19 if or when they occur,
2. monitor, detect and evaluate the contribution of AR19 to the misuse, abuse and overdose and diversion of prescription stimulants, and
3. monitor, detect and evaluate postmarketing safety signals associated with exposure to the AR19 excipient polyethylene oxide among those who intravenously administer AR19.

The report proposes a plan to monitor safety signals in routine pharmacovigilance data, several publicly available federal data sources, NPDS, and by monitoring of internet sites, local news media, and medical literature. We discuss the postmarket goals presented in this document in combination with additional key uncertainties regarding the potential public health impact of AR19 and other ADF stimulants in the FDA Briefing Document.

2.2.2.5 FDA Epidemiologic Data Sources and Analyses

2.2.2.5.1 The National Survey on Drug Use and Health

Data Source: Maintained by the Substance Abuse and Mental Health Services Administration (SAMHSA), the National Survey on Drug Use and Health (NSDUH) is an annual cross-sectional survey of the civilian, non-institutionalized U.S. population aged 12 years or older. Each year approximately 70,000 individuals are surveyed using a multistage area probability sampling strategy designed to be representative of the general U.S. population. Data are collected using audio assisted self-interviewing of residents of households and non-institutional group quarters (e.g., shelters, rooming houses, dormitories) and from civilians living on military bases. The survey excludes homeless persons who do not use shelters, military personnel on active duty, and residents of institutional group quarters, such as jails and hospitals. The survey provides national estimates, based on respondents' self-reported drug taking behaviors, including the prevalence of NMU of prescription stimulants (e.g., amphetamine products, methylphenidate products, anorectic (weight-loss) stimulants, Provigil®) and prescription pain relievers (e.g., hydrocodone, oxycodone, tramadol, codeine, morphine, fentanyl, buprenorphine, oxymorphone, Demerol®, hydromorphone, methadone, and other prescription pain relievers).

Definitions:

- **Use:** Any use (i.e., for any reason) of specific prescription drugs in the past 12 months
- **Misuse:** NSDUH defines *misuse* of a drug as the following: "use in any way not directed by a doctor, including use without a prescription of one's own; use in greater amounts, more often, or longer than told." Since NSDUH's definition of misuse includes intentional, non-therapeutic use of a drug to obtain a desired psychological or physiological effect (i.e., abuse), this review labels it *NMU*.

Search Parameters and Data Analysis: The 2015 survey underwent a major questionnaire redesign that included more detailed questions on past-year use and NMU of prescription drugs and the reasons for NMU. For this reason, we restricted the extraction of relevant information to detailed NSDUH data tables

and reports published online by SAMHSA between 2015 and 2018.² Data were abstracted on overall and age-specific national estimates of past-year use and NMU of prescription stimulants, as well as the source and reason for the most recent NMU event. In general, results were reported for all prescription stimulants and, where noted, by specific prescription stimulant API. Analogous information was abstracted on overall prescription pain relievers, which are largely comprised of prescription opioid analgesics, to provide context as this is the only class of drugs that has some products currently labeled as having properties expected to deter abuse via certain routes. For the most recent available year of data from NSDUH (2018), past-year polysubstance drug use was examined for selected substances (e.g., alcohol, tobacco, marijuana, opioids, pain relivers, methamphetamine, tranquilizers, benzodiazepines, sedatives, cocaine) with prescription stimulant NMU using the crosstab analyses tool made available by the Public-use Data Analysis System provided by SAMHSA.³ The crosstab analyses tool was also used to examine the estimated percentage of individuals who initiated prescription stimulant or pain reliever NMU in the past year. Results were reported in terms of percent of the total population, and percent of past-year any-users.

2.2.2.5.2 Monitoring the Future

Data Source: Supported by the National Institute on Drug Abuse and conducted by the University of Michigan, Monitoring the Future (MTF) is an annual cross-sectional survey of adolescent, college, and adult high school students and graduates conducted continuously since 1975. The purpose of MTF is to monitor emerging substance abuse problems and understand the effectiveness of policy and intervention efforts designed to address them. The main component of the survey captures self-reported drug use behaviors in a nationally representative sample of public and private secondary school students enrolled in the eighth, tenth, and twelfth grade. In 2019 the survey included approximately 42,500 students. This school-based survey asks about use of a wide variety of substances, including alcohol, tobacco, and other over-the-counter, prescription, and illicit drugs. Specifically, the survey asks about NMU of several stimulants and other prescription drugs, that is, “use outside of a doctor’s orders.” The MTF survey categorizes prescription stimulants into an overall amphetamine category that includes multiple stimulant drug terms (e.g., uppers, ups, speed, dexies, pep pills, diet pills, meth or crystal meth) and Brand name drugs (e.g., Dexedrine, Ritalin, Adderall, Concerta, Vyvanse, Methamphetamine). Stimulant product-specific results are also ascertained by the MTF survey for Adderall, Ritalin, and Methamphetamine.

Definitions:

- **Use:** MTF defines *use* of a drug as the following: On your own—that is, without a doctor telling you to take them. Since MTF definition of misuse includes intentional, non-therapeutic use of a drug to obtain a desired psychological or physiological effect (i.e., abuse), this review labels it *NMU*.

Search Parameters and Data Analysis: Published results were extracted on the annual prevalence of NMU for various substances (e.g., alcohol, tobacco, marijuana, amphetamines, tranquilizers, cocaine, various opioids). Our analysis was restricted from 2013 through 2019 because of a change in the language used in the questionnaire pertaining to amphetamine NMU that occurred in 2013.⁴ Values were reported for each substance in terms of percent of the total population for the eighth, tenth, and twelfth grades combined.

² National Survey on Drug Use and Health (NSDUH). Annual Detailed Tables. Available at: <https://www.samhsa.gov/data/data-we-collect/nsduh-national-survey-drug-use-and-health>. (accessed August 25, 2020).

³ Public-use Data Analysis System (PDAS), the online tool for Substance Abuse and Mental Health Data Archive (SAMHDA) studies. Available at: <https://pdas.samhsa.gov/#/>. (accessed August 25, 2020).

⁴ Monitoring the Future national survey results on drug use, 1975-2019: Overview, key findings on adolescent drug use. Available at: <http://www.monitoringthefuture.org/pubs.html#monographs>, (accessed August 25, 2020).

2.2.2.5.3 American Association of Poison Control Centers, National Poison Data System

Data Source: Maintained by the American Association of Poison Control Centers (AAPCC), NPDS cases capture data from calls to U.S. poison control centers (PCCs) on a near real-time basis from the public, healthcare professionals, and other individuals regarding exposures to prescription drugs, over-the-counter medications, foods, and unapproved products.⁵ As of 2018, NPDS data came from fifty-five PCCs and covered the entire U.S. population.⁶ PCCs receive calls for exposures to substances through the Poison Help Line 24 hours per day, offer medical advice, and document events in the database. PCC healthcare professionals systematically follow-up on exposures to document their medical outcome. Quality control measures are used to ensure data accuracy and completeness.

Calls to U.S. PCCs for exposures may result in documentation of an event, provision of information, or advice regarding medical management, and AAPCC staff managing these calls undergo training in the efforts to standardize documentation across centers. Documentation of calls in NPDS case records may include detailed product-specific information on one or more substances as well as patient demographics, the reason for exposure and route(s) of use, the medical outcome severity and clinical effects of the exposure, the level of care received, and other variables such as “relatedness,” which requires manual chart review to determine the relatedness of the exposure to the outcomes of interest. It is important to note that these details are only available if the information is provided by the caller; some callers are not necessarily experiencing symptoms or side effects when they call, and the AAPPC does not completely verify the accuracy of the information from every call made to a member center. Additional exposures may not be documented in calls to PCCs, and the calls to PCCs represent an unknown proportion of all NMU of prescription and illicit stimulants.⁶

In 2018, there were almost 2.1 million closed human exposure cases logged at PCCs and included in NPDS.⁶ Almost 59% of cases were for individuals under the age of 20 years, and over 17% of cases were for adolescents and young adults between the ages of 13 and 29 years. Over 76% of cases involved unintentional exposures, 19% of cases involved intentional exposures, with “*intentional – misuse*” and “*intentional – abuse*” exposure reasons (referred to as “NMU” throughout the rest of this epidemiologic data review) accounting for only 5% of all closed human exposures, and the remainder documented other reasons. An oral (ingestion) route of exposure was documented in over 83% of cases, an inhalation/nasal route of exposure was documented in over 6% of cases, and an injection (parenteral) route of exposure was documented in almost 1% of cases.

Definitions: Key variables are defined below. Additional detail regarding the definitions of other variables are provided in **Table 71** in **Section 4.6**.

- **Exposure Reasons:**
 - **Intentional – Misuse:** “An exposure resulting from the intentional improper or incorrect use of a substance for reasons other than the pursuit of a psychotropic effect.”
 - **Intentional – Abuse:** “An exposure resulting from the intentional improper or incorrect use of a substance where the victim was likely attempting to gain a high, euphoric effect, or some other psychotropic effect.” This includes recreational use of a substance for any effect.
 - **NMU:** Defined as Intentional – Misuse or Intentional – Misuse.
- **Exposure Route:**
 - **Ingestion (oral):** An exposure by the oral route.

⁵ American Association of Poison Control Centers, National Poison Data System (NPDS). Available at: <https://aapcc.org/national-poison-data-system>. (accessed August 25, 2020).

⁶ Gummin DD, Mowry JB, Spyker DA, Brooks DE, Beuhler MC, Rivers LJ, Hashem HA, and Ryan ML. 2018 Annual Report of the American Association of Poison Control Centers’ National Poison Data System (NPDS): 36th Annual Report. *Clinical Toxicology*. 2019; 57 (12): 1220-1413.

- **Inhalation/Nasal:** An exposure by the pulmonary route (tracheal or nasal). This includes nasal insufflation of substances.
- **Parenteral (injection):** An exposure resulting from the injection of a substance into the body.
- **Medical Outcome:**
 - **Minor Effect:** The patient exhibited some symptoms as a result of the exposure, but they were minimally bothersome to the patient. The symptoms usually resolve rapidly and often involve skin or mucous membrane manifestations. The patient has returned to a pre-exposure state of well-being and has no residual disability or disfigurement.
 - **Moderate Effect:** The patient exhibited symptoms as a result of the exposure which are more pronounced, more prolonged or more of a systemic nature than minor symptoms. Usually some form of treatment is or would have been indicated. Symptoms were not life-threatening, and the patient has returned to a pre-exposure state of well-being with no residual disability or disfigurement.
 - **Major Effect:** The patient has exhibited symptoms as a result of the exposure which were life-threatening or resulted in significant residual disability or disfigurement.
 - **Death:** The patient died as a result of the exposure or as a direct complication of the exposure where the complication was unlikely to have occurred had the toxic exposure not preceded the complication.

Search Parameters and Data Analysis: Closed human exposure cases were assessed for prescription and illicit stimulants as well as polysubstance use of prescription and illicit stimulants with other selected drugs and other substances of interest such as opioid analgesics and alcohol (**Table 3**). The search criteria was defined by identifying generic codes and product codes for pharmaceutical preparations containing amphetamine, dextroamphetamine, mixed amphetamine salts, lisdexamfetamine, methylphenidate, dexmethylphenidate, methamphetamine, and cocaine, and illicit stimulant drugs containing amphetamine, methamphetamine, and cocaine using Micromedex® Solutions and the 2019 AAPCC Pharmaceutical and Non-Pharmaceutical Generic Code List – February 2019 version (product codes are included in **Table 69** in **Section 4.6**). Generic and/or product codes were identified for pharmaceutical preparations containing opioids (including cough and cold preparations and anti-diarrheals), illicit opioids (including illicit fentanyl, non-prescription synthetic opioid analgesics, other/unknown narcotics, and heroin), benzodiazepines, muscle relaxants, alcohol, and cannabis using the 2019 AAPCC Pharmaceutical and Non-Pharmaceutical Generic Code List – February 2019 version (generic and product codes are included in **Table 70** in **Section 4.6**). Data were abstracted on closed, human exposure cases with prescription and illicit stimulants and use of stimulants with prescription and illicit opioids (January 1, 2001 to December 31, 2018) on December 11, 2019. Search parameters used for prescription and illicit stimulants and other selected drugs and substances are summarized in **Table 4**.

Table 3. Prescription stimulants, illicit stimulants, and other selected drugs and substances

CII Prescription and Illicit Stimulants	Other Selected Drugs and Substances
Prescription Stimulants* <ul style="list-style-type: none"> • Specific additional analyses for: <ul style="list-style-type: none"> ○ Amphetamine ○ Dextroamphetamine ○ Mixed Amphetamine Salts ○ Lisdexamfetamine ○ Methylphenidate ○ Dexmethylphenidate ○ Methamphetamine 	Prescription Opioid Analgesics <ul style="list-style-type: none"> • Specific additional analyses for: <ul style="list-style-type: none"> ○ Oxycodone ○ Hydrocodone ○ Morphine ○ Tramadol ○ Codeine
Illicit Stimulants <ul style="list-style-type: none"> • Specific additional analyses for: <ul style="list-style-type: none"> ○ Cocaine** 	Illicit Opioids***

○ Methamphetamine	
Amphetamine NOS****	Any Benzodiazepine
	Any Muscle Relaxant
	Any Alcohol
	Any Cannabis

CII, Schedule II; NOS, not otherwise specified.

Note: '*' Prescription stimulants include the following CII stimulants: amphetamine, dextroamphetamine, mixed amphetamine salts, lisdexamfetamine, methylphenidate, dexmethylphenidate, and methamphetamine. Other stimulants, such as caffeine, ephedrine, or products indicated solely for weight loss (e.g., phentermine) are excluded.

Note: '**' Regulated pharmaceutical cocaine is unlikely to be found outside of the hospital setting, since it is primarily used in the surgical setting. Therefore, all regulated pharmaceutical cocaine was treated as illicit cocaine.

Note: '***' Illicit opioids include illicit fentanyl, non-prescription synthetic opioid analgesics, other/unknown narcotics, and heroin.

Note: '****' Amphetamine NOS includes amphetamine products where it was unclear if it was a prescription product or illicitly manufactured.

Table 4. NPDS search parameters – prescription and illicit stimulants and other selected drugs and substances

Report Name	Case Log (Generic Code/Product Code); Case Log (Product Code)
Month/Year of Query	December 2019
Date Range for Query	January 1, 2001–December 31, 2018
Location	50 U.S. States, Washington DC, Overseas U.S. Military/Diplomatic, Refused to Give, Unknown, Other U.S. Territory, Puerto Rico, U.S. Virgin Islands, American Samoa, Guam, Northern Marianas
Call Type	Exposure
Case Status	Closed
Species	Human

DC, District of Columbia; NPDS, National Poison Data System; U.S., United States.

Prescription and illicit stimulants were categorized through a manual review of drug codes. Stimulant products were classified as prescription stimulants if there was an associated Brand name and/or manufacturer name, strength, or formulation documented in addition to the API mentioned in the call. For all prescription stimulant products other than amphetamine and methamphetamine, it was assumed that any slang or chemical name linked to these APIs were more likely to be diverted than illicitly manufactured. For cocaine, regulated pharmaceutical cocaine is unlikely to be found outside of the hospital setting since it is primarily used in the surgical setting. There were also very few regulated pharmaceutical cocaine cases. Therefore, all regulated pharmaceutical cocaine exposures were treated as illicit cocaine. Illicit methamphetamine was identified by slang terms and chemical names without additional manufacturer details associated with the product. There were also a number of amphetamine drug mentions where it was unclear if amphetamine was a prescription product or illicitly manufactured. These products were classified as amphetamine, not otherwise specified (NOS). Stimulant drug codes were manually screened and categorized if there were also prescription or illicit opioid products included in the stimulant drug code. Additional information on the inclusion, exclusion, and categorization of stimulant codes is included in **Table 68** in **Section 4.6**.

Analysis of NPDS consisted of three main components, with multiple sub-components:

- Evaluation of exposures by exposure reason for overall stimulant categories and prescription stimulant APIs
 - Exposure cases involving prescription and illicit stimulants were aggregated for the eighteen-year period (2001–2018). Data was then stratified by reason for exposure (NMU, intentional – suspected suicide, intentional – unknown; unintentional, adverse reaction, and other/unknown).
- Cases of NMU
 - Trends in overall exposures

- Annual counts of exposure cases were stratified by overall stimulant categories and by individual prescription stimulant APIs.
- By age
 - Exposure cases involving stimulant categories were aggregated for the eighteen-year period and stratified by age group.
- Trends in exposures by age
 - Annual counts of prescription stimulant exposure cases were stratified by age.
- By region
 - Data on exposure cases for overall stimulant categories were aggregated for the eighteen-year period and stratified by region (see **Table 72** in **Section 4.6** for detailed information on which states were included in each region).
- By route of exposure
 - Data on exposure cases for overall stimulant categories and individual prescription stimulant APIs were aggregated for the eighteen-year period and stratified them by route of exposure. In NPDS data, the route of administration is not captured specifically for each substance documented in a multi-substance exposure case, and multiple routes can be documented for a single substance. Therefore, data were restricted to cases involving only a single substance, and for these cases, each route mentioned by the caller was counted separately. As a result, the totals for each individual route may exceed the total number of exposure cases for that substance.
- By medical outcome
 - Data on single-substance exposure cases were aggregated for overall stimulant categories and individual prescription stimulant APIs for the eighteen-year period and stratified by related medical outcome from a related clinical effect. NPDS defines related clinical effects as exposures where the following criteria are satisfied: the timing and severity of clinical effects are reasonable for the reported exposure, the clinical effect is consistent with the anticipated substance, and the clinical assessment is made by a physician.
- By clinical outcome
 - Data on single-substance exposure cases for stimulant categories and individual prescription stimulant APIs were aggregated for the eighteen-year period and stratified by the top ten related clinical effects.
- Route of exposure by medical outcome
 - Data on single-substance exposure cases for prescription stimulants were aggregated for the eighteen-year period and stratified by route of exposure and related medical outcome.
- By polysubstance use
 - Data on multi-substance exposure cases for overall stimulant categories and individual prescription stimulant APIs were aggregated for the eighteen-year period and stratified by polysubstance use (prescription and illicit opioids, illicit stimulants, benzodiazepines, muscle relaxants, cannabis, and alcohol).
- Contextual analysis of opioid analgesics
 - NMU cases by route of exposure
 - Data on single-substance exposure cases for prescription stimulants (2001–2018), other selected opioid analgesics including oxycodone, hydrocodone, morphine,

tramadol, and codeine (2014–2018),⁷ and different formulations of oxycodone (2012–2017)⁸ were aggregated and stratified by route of exposure.

All NPDS results were replicated independently using the same criteria by two separate analysts to ensure accuracy of the results, with any discrepancies resolved by a detailed review of processes.

2.2.2.5.4 National Electronic Injury Surveillance System – Cooperative Adverse Drug Event Surveillance

Data Source: The number of surveillance cases and national estimates of the number of emergency department (ED) visits for drug-related AEs were assessed from the National Electronic Injury Surveillance System – Cooperative Adverse Drug Event Surveillance (NEISS-CADES) project, a national stratified probability sample of approximately sixty hospitals with a minimum of six beds and a 24-hour ED in the United States and its territories. The NEISS-CADES project, which has been described in detail elsewhere, is a joint effort of the Centers for Disease Control and Prevention (CDC), the U.S. Consumer Product Safety Commission, and FDA.^{9,10,11,12} In brief, trained coders located at each participating hospital review clinical records of every ED visit to identify clinician-diagnosed drug related AEs, to document up to four medications implicated in each AE, and to record narrative descriptions of the incident (including clinical diagnoses, manifestations, and concurrent substance use). Pharmaceutical products captured in NEISS-CADES include: prescription and over-the-counter medications, vaccines/immunizations, vitamins/minerals, and herbal/complementary nutritional products. It is important to note that cases involving ED visits for harms *only* from illicit drugs are not included in the source data. In order to calculate national estimates, each case is assigned a sample weight based on the inverse probability of selection. The sample weights include adjustments for changes in the hospital population (e.g., non-response, mergers, and closures) and for the annual number of ED visits in the United States. Estimates based on <20 cases or total estimates <1200 are considered statistically unstable and are not shown. Estimates with coefficient of variation >30% may be statistically unstable and are noted.

Definitions: NEISS-CADES has historically focused exclusively on ED visits due to use of medications for a therapeutic indication, or unintended medication exposures by young children. However, in 2016, NEISS-CADES surveillance activities were expanded to represent the full spectrum of pharmaceutical-

⁷ 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).

⁸ 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[^] among individuals 12 years of age and older. Page 17. Available at: <https://www.fda.gov/media/134150/download>. (accessed July 10, 2020).

⁹ Budnitz DS, Pollock DA, Weidenbach KN, Mendelsohn AB, Schroeder TJ, Annest JL. National surveillance of emergency department visits for outpatient adverse drug events. *JAMA*. 2006; 296 (15): 1858-1866.

¹⁰ Jhung MA, Budnitz DS, Mendelsohn AB, Weidenbach KN, Nelson TD, Pollock DA. Evaluation and overview of the National Electronic Injury Surveillance System-Cooperative Adverse Drug Event Surveillance Project (NEISS-CADES). *Med Care*. 2007; 45 (10 Supl 2): S96-102.

¹¹ Schroeder TJ, Ault K. National Electronic Injury Surveillance System (NEISS) sample design and implementation from 1997 to present. 2001. Available at: https://www.cpsc.gov/s3fs-public/pdfs/blk_media_2001d011-6b6.pdf. (accessed August 25, 2020).

¹² Shehab N, Lovegrove MC, Geller AI, Rose KO, Weidle NJ, Budnitz DS. US Emergency Department Visits for Outpatient Adverse Drug Events, 2013-2014. *JAMA*. 2016; 316 (20): 2115-2125.

related harm, encompassing ED visits resulting from therapeutic use, and in addition, self-harm and NMU. NMU includes visits for abuse, therapeutic misuse, and overdoses without indication of intent (**Table 5**). **Section 4.7** provides the definitions for the intents of drug use (nonmedical, therapeutic, and self-harm).

Table 5. NEISS-CADES definition of NMU of drugs^{13,14}

Category	NEISS-CADES Definition
Abuse	Clinician diagnosis of abuse (for current ED visits) or documented recreational use (e.g., “to get high”)
Therapeutic misuse	Documented therapeutic intent, but the pharmaceutical was not used as directed (e.g., taking someone else’s prescription medication for pain, intentionally taking larger doses than prescribed or recommended)
Overdoses without indication of intent	Cases of overdose without indication of intent have insufficient documentation to categorize the case as abuse, therapeutic, or self-harm (e.g., patients found unresponsive by paramedics and patients unable or unwilling to provide description of circumstances or intent). Section 4.7 provides definitions for intent of drug use.

ED, emergency department; NEISS-CADES, National Electronic Injury Surveillance System – Cooperative Adverse Drug Event Surveillance; NMU, nonmedical use.

Search Parameters and Data Analysis: Analyses of 2016 through 2018 NEISS-CADES data were conducted and provided to FDA by the CDC Division of Healthcare Quality Promotion. Cases included ED visits from 2016 through 2018 for harms from prescription stimulant products as well as from polysubstance use of CII stimulant products and other substances (e.g., prescription opioid analgesics, benzodiazepines, alcohol, cocaine, heroin). Specific clinical manifestations documented during ED visits from 2016 through 2018 for harms from NMU of CII prescription stimulant products were also provided. We abstracted relevant data and reported overall annual estimates of AEs involving CII prescription stimulants and prescription medications other than CII prescription stimulants; annual estimates of AEs involving NMU, therapeutic use, and/or self-harm use of prescription stimulants by age, API, and polysubstance use; and annual estimates of documented clinical manifestations resulting from NMU of CII prescription stimulants.

2.2.2.5.5 NEISS-CADES Data Comparing ED Visits for NMU of Prescription Stimulants and other Pharmaceutical Products from Geller et al., 2019¹³

Data Source: Funded by U.S. Department of Health and Human Services and conducted through a collaboration with CDC and FDA, this published study by Geller et al. in 2019 analyzed NEISS-CADES data to describe ED visits for AEs involving pharmaceuticals, including prescription stimulants. This analysis included 5,130 surveillance cases from 56 EDs from January 1, 2016 through December 31, 2016. From these surveillance cases, there were an estimated 358,247 ED visits for harms involving NMU of pharmaceuticals and an estimated 1,474,556 ED visits for harms involving therapeutic use of pharmaceuticals. Over 83% of NMU visits involved either abuse (39.7%) or overdoses without indication of therapeutic intent, abuse, or self-harm (43.7%), while the remaining 16.6% of visits involved therapeutic misuse. A detailed description of the data source, NEISS-CADES, and the definitions of NMU can be found in **Section 2.2.2.5.4, above**.

¹³ Geller AI, Dowell D, Lovegrove MC, et al. U.S. Emergency Department Visits Resulting From Nonmedical Use of Pharmaceuticals, 2016. *Am J Prev Med.* 2019; 56 (5): 639-647.

¹⁴ Lovegrove MC, Dowell D, Geller AI, et al. US Emergency Department Visits for Acute Harms From Prescription Opioid Use, 2016-2017. *Am J Public Health.* 2019; 109 (5): 784-791.

Search Parameters and Data Analysis: Relevant results were abstracted from tables and figures provided in the final published study. These data included surveillance case counts and overall annual estimates of ED visits for AEs involving CII prescription stimulants to provide insight into harms associated with NMU of prescription stimulants. Surveillance case counts and overall annual estimates of ED visits for AEs involving prescription opioid analgesics were also included to provide context for the harms related to NMU of prescription opioid analgesics.

2.2.2.5.6 The Treatment Episode Data Set

Data Source: Also maintained by SAMHSA, the Treatment Episode Data Set (TEDS) is an admission-based census that includes facilities that receive public funds, are licensed or certified by states to provide treatment, or are tracked at the state level for other reasons. It provides information on demographic and substance abuse characteristics for individuals aged 12 years and older who are admitted for abuse of alcohol and/or drugs in facilities that report to state administrative data systems. Although TEDS collects information from all states, each state varies in the information that it submits; private facilities, doctor's practices, and specific other types of facilities (e.g., programs within the criminal justice system, detox facilities) may not be required to report. The TEDS dataset lists the primary, secondary, and tertiary substances of NMU reported by those entering treatment, and this information is, in general, only available at the molecular level (i.e., brand and formulation data are not available).

Definitions:

- **Primary, secondary, and tertiary substances:** are those substances reported to TEDS that led to the treatment episode and are not necessarily a complete enumeration of all drugs used at the time of admission.
- **Stimulants:** Included methamphetamine, other amphetamines, and other stimulants.
 - **Other Amphetamines:** Included amphetamines, 3,4-methylenedioxy-methamphetamine (MDMA), phenmetrazine, and other unspecified amines and related drugs.
 - **Other Stimulants:** Included methylphenidate and any other stimulants.

Search Parameters and Data Analysis: Published results were abstracted from the 2017 TEDS report published online by SAMHSA.¹⁵ These data included the percentage of substances (e.g., stimulants, alcohol, opiates, cocaine, marijuana, and other drugs) cited as the primary reason for TEDS admission. For stimulants, overall as well as stratified results were included for methamphetamine, other amphetamines, and other stimulants. Yearly percentage values were reported for each substance in terms of percent of the total TEDS population for 2007–2017.

2.2.2.5.7 National Addictions Vigilance Intervention and Prevention Program

Data Source: Inflexxion, Inc., a subsidiary of IBH Solutions, operates NAVIPPRO®, a product-specific surveillance system that consists of multiple data streams for monitoring prescription drug NMU.¹⁶ One of these streams is the ASI-MV®, a computer-administered self-report version of the Addiction Severity Index assessment tool, which measures addiction severity and includes questions relating to use or NMU of specific products such as route of administration and the source of the prescription medication in near real-time. The study population consists of a convenience sample of adults seeking treatment or being assessed for substance use disorder treatment at participating facilities across the United States. In 2018,

¹⁵ Treatment Episode Data Set (TEDS). Annual Report. Available at: <https://www.samhsa.gov/data/data-we-collect/teds-treatment-episode-data-set>. (accessed August 25, 2020).

¹⁶ Butler SF, Budman SH, Licari A, et al. National addictions vigilance intervention and prevention program (NAVIPPRO™): a real-time, product-specific, public health surveillance system for monitoring prescription drug abuse. *Pharmacoepidemiol Drug Saf*. 2008; 17 (12): 1142-1154.

NAVIPPRO® included a total of 390 treatment sites in 36 states, with variation in the adoption and use of the ASI-MV® by different states and localities.

FDA obtains surveillance data analytic reports from the NAVIPPRO® ASI-MV® every six months through an ongoing contract with Inflexxion, Inc. Each report provides estimates for the prevalence of NMU among all ASI-MV® respondents and the prevalence of NMU among ASI-MV® respondents reporting NMU for prescription opioids and heroin, by API and formulation (e.g., IR, extended-release (ER)). The first report contains information from 105,166 assessments of respondents endorsing abuse of specific opioids and routes of NMU (e.g., swallowed whole, snorting, injecting) between January 2017 and December 2018. The second report contains prevalence estimates of NMU for specific opioids in each calendar year from 2013 through 2019, which included 377-509 treatment sites in 36-41 states each year, with variation in the adoption and use of the ASI-MV® by different states and localities. In this report, numerators represent the total number of endorsements and denominators represent the total number of assessments in that calendar year. We included these data specific for opioid analgesics to be able to put information regarding prescription stimulant NMU collected from AR19.MA003 in context, since opioid analgesics are currently the only class of drugs that has some products currently labeled as having properties expected to deter abuse via certain routes.

Definitions:

- **NMU:** Determined by an algorithm from responses given during a computer-administered interview. The questions asked were whether the medication was obtained from their own prescription; the medication had been used via an alternate route of administration (i.e., not as prescribed); used in a way not prescribed by the doctor, but for the way it makes one feel and not for the treatment of the drug's indicated disease.
- **Any Oral Route:** Defined as swallowing whole.
- **Any Non-Oral Route:** Defined as snorting or injecting.

Search Parameters and Data Analysis: Data from the first report was used to assess the prevalence of NMU by route of administration (e.g., swallowed whole, snorting, injecting) for selected prescription opioid analgesics (oxycodone, hydrocodone, morphine, tramadol) among respondents reporting product-specific NMU from 2017 through 2018 to provide context for NMU of prescription stimulants by route of administration. For the second report, our analysis was restricted from 2013 through 2017 to be most comparable to the Applicant-submitted report (AR19.MA003), which reported ASI-MV® data for prescription stimulants from 2010 through 2017. Yearly rates were reported per 100 assessments for selected prescription opioid analgesics (oxycodone, hydrocodone, morphine, tramadol).

For the trend data, FDA requests results from all sites included in ASI-MV® as well as from a consistent set of treatment centers that provided data across the entire time period. The consistent set minimizes the potential impact of treatment centers coming in and out of the sample but also drastically reduces the number of assessments included. For some drugs, geographic patterns of NMU differ substantially and the consistent set of sites may produce the most reliable trend data, although potentially less representative of people being assessed for treatment across the United States. Despite this, we reported the all-center results for prescription opioid analgesics to be consistent with the Applicant's method of including all treatment centers for the prescription stimulant analysis; however, the patterns in trends were generally consistent for the selected prescription opioid analgesics for the full set and consistent sample of treatment centers.

2.2.2.5.8 National Vital Statistics System – Multiple Cause of Death Database

Data Source: The National Vital Statistics System – Multiple Cause of Death (NVSS-MCD) Database consists of national mortality and population data, currently available for the years 1999–2019, and is

publicly accessible through the CDC.¹⁷ Data are based on death certificates for U.S. residents. Each death certificate contains a single underlying cause of death, up to twenty multiple causes, and demographic data. Data are also available on injury intent and mechanism and drug/alcohol induced causes.

Definitions:

- **Overdose deaths:** Consistent with previous literature,¹⁸ drug overdose deaths were identified using *International Classification of Diseases, Tenth Revision* (ICD-10) underlying cause-of-death codes X40–X44 (unintentional), X60–X64 (suicide), X85 (homicide), and Y10–Y14 (undetermined intent). Overdose deaths involving selected drug categories are identified by specific multiple-cause-of-death codes.
 - **Psychostimulants:** Overdoses involving prescription stimulants fall under the category “psychostimulants with abuse potential,” T43.6. Psychostimulants with abuse potential include drugs such as methamphetamine, amphetamine, and methylphenidate. Therefore, this code would include overdoses involving prescription CII stimulants indicated for ADHD (**Table 1, above**) as well as other licit stimulants such as caffeine and illicit stimulants, including methamphetamine, but not cocaine (T40.5).
 - **Opioids:** Overdoses included under opioids included heroin (T40.1); natural and semisynthetic opioids (T40.2); methadone (T40.3); and synthetic opioids excluding methadone (T40.4). The natural and semisynthetic opioids category is generally used to represent prescription opioids, although some synthetic prescription opioids, such as tramadol and fentanyl, are captured under the category for synthetic opioids excluding methadone. The large majority of deaths in the latter category are attributed to illicit fentanyl.

Search Parameters and Data Analysis: Published results were extracted from data the CDC made publicly available through the National Vital Statistics System publication, “Data Brief 356. Drug Overdose Deaths in the United States, 1999–2018.”¹⁷ Yearly number of overdose deaths that involved psychostimulants and opioids were reported between 1999 and 2018.

2.2.2.5.9 National Data on Drug-Involved Mortality

Data Source: National data on drug-involved mortality (DIM) were made available to the Agency by the National Center for Health Statistics. Drug-involved mortality data combine the cause-of-death, demographic, and geographic information from the National Vital Statistics System – Mortality files, with information extracted from the death certificate literal text (see **Section 4.8.1** for a description of the data source). These data allow for a more granular analysis of the specific drugs involved in deaths.¹⁹ The drug-involved mortality data was sourced from National Vital Statistics System – Mortality files linked to literal text information from death certificates. The analytical dataset was constructed for analysis on October 6, 2016 as part of a previous review. This analysis could not be updated at the time of this review because access to the National Center for Health Statistics’ Research Data Center was unavailable due to the SARS-CoV-2 pandemic.

Definitions:

- **Manner of death:** Categorized according to underlying cause-of-death, coded in ICD-10. Manner of death for external injuries included unintentional deaths – V01-X59, Y85-Y86; suicide – X60-X84, Y870, *U03; homicide – X85-Y09, Y87.1, U01-U02; legal intervention – Y35, Y89.0; war – Y36,

¹⁷ Data Brief 356. Drug Overdose Deaths in the United States, 1999-2018. Available at:

https://www.cdc.gov/nchs/data/databriefs/db356_tables-508.pdf#3. (accessed August 25, 2020).

¹⁸ Warner M, Trinidad JP, Bastian BA, Miniño AM, and Hedegaard H. Drugs Most Frequently Involved in Drug Overdose Deaths: United States, 2010–2014. *Natl Vital Stat Rep.* 2016; 65 (10): 1-15.

¹⁹ Trinidad JP, Warner M, Bastian BA, Miniño AM, and Hedegaard H. Using literal text from the death certificate to enhance mortality statistics: Characterizing drug involvement in deaths. *Natl Vital Stat Rep.* 2016; 65 (9): 1-15.

- Y89.1; medical complication – Y40-Y84, Y88; and undetermined manner of death – Y10-Y34, Y87.2, Y89.9. Natural deaths (i.e., those that are not external injuries) include all other ICD-10 codes.
- **CII Stimulants:** As described in **Table 1, above**, CII stimulants included in this analysis were methamphetamine, amphetamine, methylphenidate, dextroamphetamine, dexmethylphenidate, and lisdexamfetamine (see **Section 4.8.2** for search terms for each of these drugs).

Search Parameters and Data Analysis: The drug-involved mortality data were analyzed to obtain the national count of deaths with prescription or illicit stimulant involvement among U.S. residents from years 2010 through 2014. Stimulant involvement was defined as a mention of a prescription stimulant in death certificate text, excluding mentions where information in death certificate text suggested that the stimulant was not involved in death. There were three mutually exclusive stimulant groups of interest: 1) methamphetamine, 2) amphetamine, and 3) other stimulants. We noted that methamphetamine is primarily, but not exclusively, illicitly manufactured, and that amphetamine may refer to a subgroup of CII prescription stimulant products or to both prescribed and illicit amphetamine-related drugs more broadly. Data were analyzed to determine whether drugs from one or more stimulant groups were involved in the same death. Data were further stratified the drug-involved mortality data by specific stimulant (by year), age group (number of deaths and population-adjusted rates), sex, manner of death, whether the underlying cause-of-death was a drug overdose,²⁰ and involvement of non-stimulant prescription and illicit drugs, nicotine, and alcohol.²¹ For each age group, age-specific rate of deaths were calculated by dividing the average annual number of deaths with stimulant involvement by the annual average population size during years 2010 through 2014.

2.2.3 Pharmacovigilance Methods and Materials

2.2.3.1 Case Definition

We searched the FDA Adverse Event Reporting System (FAERS) database and medical literature to identify postmarketing case reports of nonmedical CII prescription stimulant use via a non-oral route. Although the focus of this review was to identify non-oral NMU, we included cases of CII prescription stimulant NMU via “chewing” if the product is not approved as a chewable formulation, or cases of “cooking” or “baking” as a non-prescribed method of preparation for oral tablets or capsules. FAERS reports of nonmedical oral CII prescription stimulant use, such as off-label usage for an unapproved indication or oral overdose, were not included in our case series for a hands-on analysis; however, a high-level overview of these reports was provided.

Inclusion criteria

We included cases reporting NMU of CII prescription stimulants listed in **Table 1** via a non-oral route. This included cases of non-oral NMU, as well as cases of ingestion by chewing a product not approved as a chewable formulation or following cooking or baking oral tablets or capsules. Although not the focus of this review, we included any cases of NMU of methylphenidate transdermal system via a non-prescribed route for completeness.

Exclusion criteria

- Report of nonmedical CII prescription stimulant use but route of NMU was unknown.

²⁰ Consistent with published literature (Warner et al., 2016), overdose was defined by the underlying ICD-10 cause-of-death: X40, X41, X42, X43, X44, X60, X61, X62, X63, X64, X85, Y10, Y11, Y12, Y13, or Y14.

²¹ In determining involvement of alcohol, nicotine, and drugs other than the stimulants of interest, the following terms for drugs were not included: chemical, drug, intoxicant, medicine, narcotic, pharmaceutical, polypharmacy, stimulant, substance, and each of the stimulants of interest. These terms were not included because they could have referred to the stimulant drugs of interest.

- Report of NMU of a known illicit (non-prescription) stimulant (e.g., illicit methamphetamine, synthetic stimulants (bath salts), 3,4-methylenedioxy-methamphetamine (MDMA), etc.).
- Report of accidental exposure or overdose due to medication error or product quality issue.
- Lacked narrative to suggest nonmedical CII prescription stimulant use.

2.2.3.2 FAERS Search Strategy

DPV searched the FAERS database in 2017 and 2020 with the strategies described in **Table 6**.

Table 6. FAERS* search strategy

Dates of search	March 15, 2017	April 24, 2020
Time periods of search	January 1, 2007–December 31, 2016	January 1, 2017–April 23, 2020
Search types	FDA Business Intelligence Solution Quick Query and Product-Manufacturer Reporting Summary	FDA Business Intelligence Solution Quick Query Mercado Quick Search
Product terms [†]	Amphetamine; Amphetamine adipate; Amphetamine adipate\dextroamphetamine; Amphetamine aspartate; Amphetamine aspartate monohydrate\amphetamine sulfate\dextroamphetamine saccharate\ dextroamphetamine sulfate; Amphetamine aspartate\amphetamine sulfate\dextroamphetamine saccharate\dextroamphetamine sulfate; Amphetamine aspartate\dextroamphetamine saccharate; Amphetamine hydrochloride; Amphetamine phosphate; Amphetamine sulfate; Amphetamine sulfate\dextroamphetamine; Amphetamine\dextroamphetamine; Dexmethylphenidate; Dexmethylphenidate hydrochloride; Dextroamphetamine; Dextroamphetamine hydrochloride; Dextroamphetamine saccharate; Dextroamphetamine sulfate; Lisdexamfetamine; Lisdexamfetamine dimesylate; Methamphetamine; Methamphetamine hydrochloride; Methamphetamine saccharate; Methylphenidate; Methylphenidate hydrochloride	
MedDRA search terms	<i>Drug abuse and dependence (SMQ)</i> Broad search [‡] (Version 19.1)	<i>Drug abuse and dependence (SMQ)</i> Broad search [‡] (Version 23.0)
Country, derived	All	U.S.

FDA, Food and Drug Administration; FAERS, FDA Adverse Event Reporting System; MedDRA, Medical Dictionary for Regulatory Activities; SMQ, Standardized MedDRA Query; U.S., United States.
Note: '*' See **Section 4.3** for a description of the FAERS database.
Note: '†' 2017 search did not include the Product Active Ingredient Dexmethylphenidate.
Note: '‡' See **Section 4.4** for a list of Preferred Terms within the SMQ.
Source: FDA Adverse Event Reporting System.

After we retrieved reports using the search strategies in **Table 6, above**, we filtered the reports using narrative text search for reports of NMU via non-oral routes with the keywords: *chew, cook, inhal, inject, insuffl, intrav, nasal, shoot, smoke, snort*.

2.2.3.3 Literature Search

We searched the medical literature with the strategy described in **Table 7**. The purpose of this literature search was to identify any case reports associated with nonmedical CII prescription stimulant use, as well as to summarize the published findings on the morbidity related to nonmedical CII prescription stimulant use.

Table 7. Literature search strategy

Date of search	April 13, 2020
Database	PubMed@FDA, EMBASE

Search terms	[Stimulant OR Methylphenidate OR Amphetamine] AND [Abuse OR Misuse OR Addiction]
Years included in search	From 1971 to date of search
Other criteria:	Articles in English; Human studies or summaries of findings in humans

3 RESULTS

3.1 DRUG UTILIZATION RESULTS

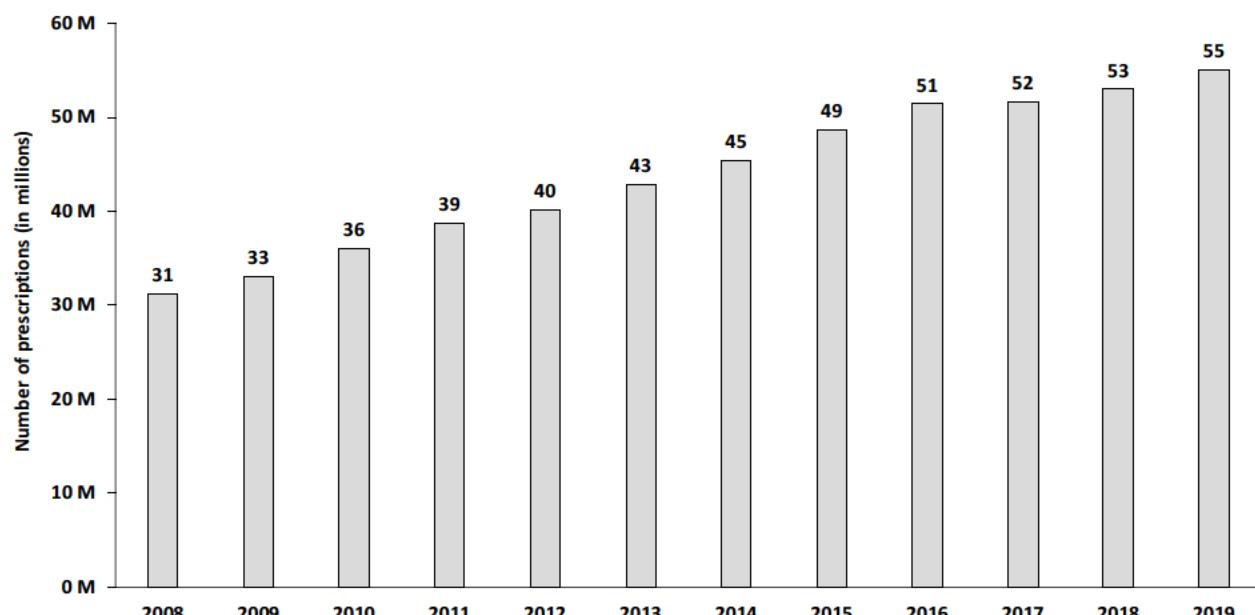
3.1.1 Settings of Care

In 2019, approximately 93% of CII prescription stimulant products were distributed to U.S. outpatient retail pharmacies, followed by 5% to non-retail pharmacies, and 2% to mail-order/specialty pharmacies.²² As a result, we focused our analyses on the U.S. outpatient retail pharmacy settings only.

3.1.2 Prescription Data from U.S. Outpatient Retail Pharmacies

Figure 1 below and Table 64 in Section 4.2 shows national estimates of prescriptions dispensed for CII stimulants from U.S. outpatient retail pharmacies from 2008 to 2019. Prescriptions for CII stimulants increased 76% from approximately 31 million prescriptions in 2008 to 55 million prescriptions in 2019.

Figure 1. National estimates of prescriptions dispensed for CII stimulants from U.S. outpatient retail pharmacies from January 2008 through December 2019



CII, Schedule II; U.S., United States.

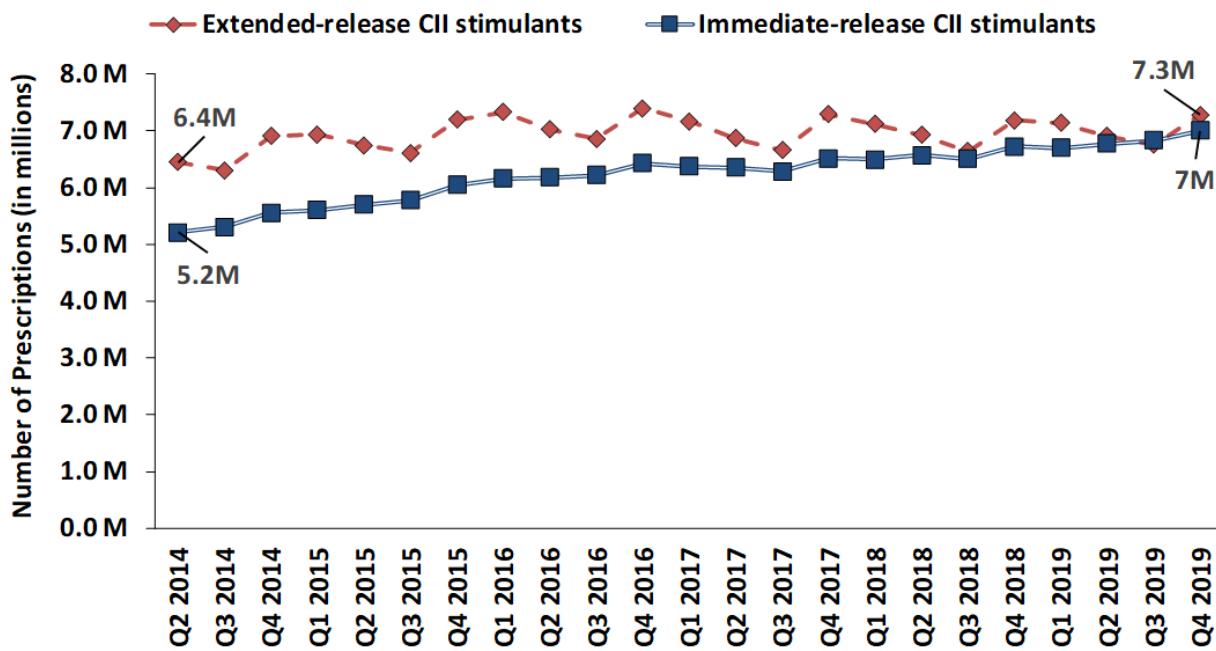
Source: FDA analysis of IQVIA, National Prescription Audit™. 2008-2019. Extracted April 2020. File: 2020-95 NPA stimulants Apr-2020.xlsx.

Analysis of recent time periods were conducted to assess more granular data. National estimates of prescriptions dispensed for IR and ER CII stimulants from U.S. outpatient retail pharmacies increased from the second quarter of 2014 through the fourth quarter of 2019 (**Figure 2, below** and **Table 60 in Section 4.2**). Prescriptions dispensed for IR CII stimulants increased 34% from 5.2 million prescriptions

²² IQVIA, National Sales Perspectives™. 2019. Extracted April 2020. File 2020-95 NSP- setting of care_1_Mar-13-2020.xlsx.

in the second quarter of 2014 to 7 million prescriptions in the fourth quarter of 2019, and prescriptions dispensed for ER CII stimulants increased 14% from 6.4 million prescriptions in the second quarter of 2014 to 7.3 million prescriptions in the fourth quarter of 2019.

Figure 2. National estimates of prescriptions dispensed for IR and ER CII stimulants from U.S. outpatient retail pharmacies from the second quarter of 2014 through the fourth quarter of 2019

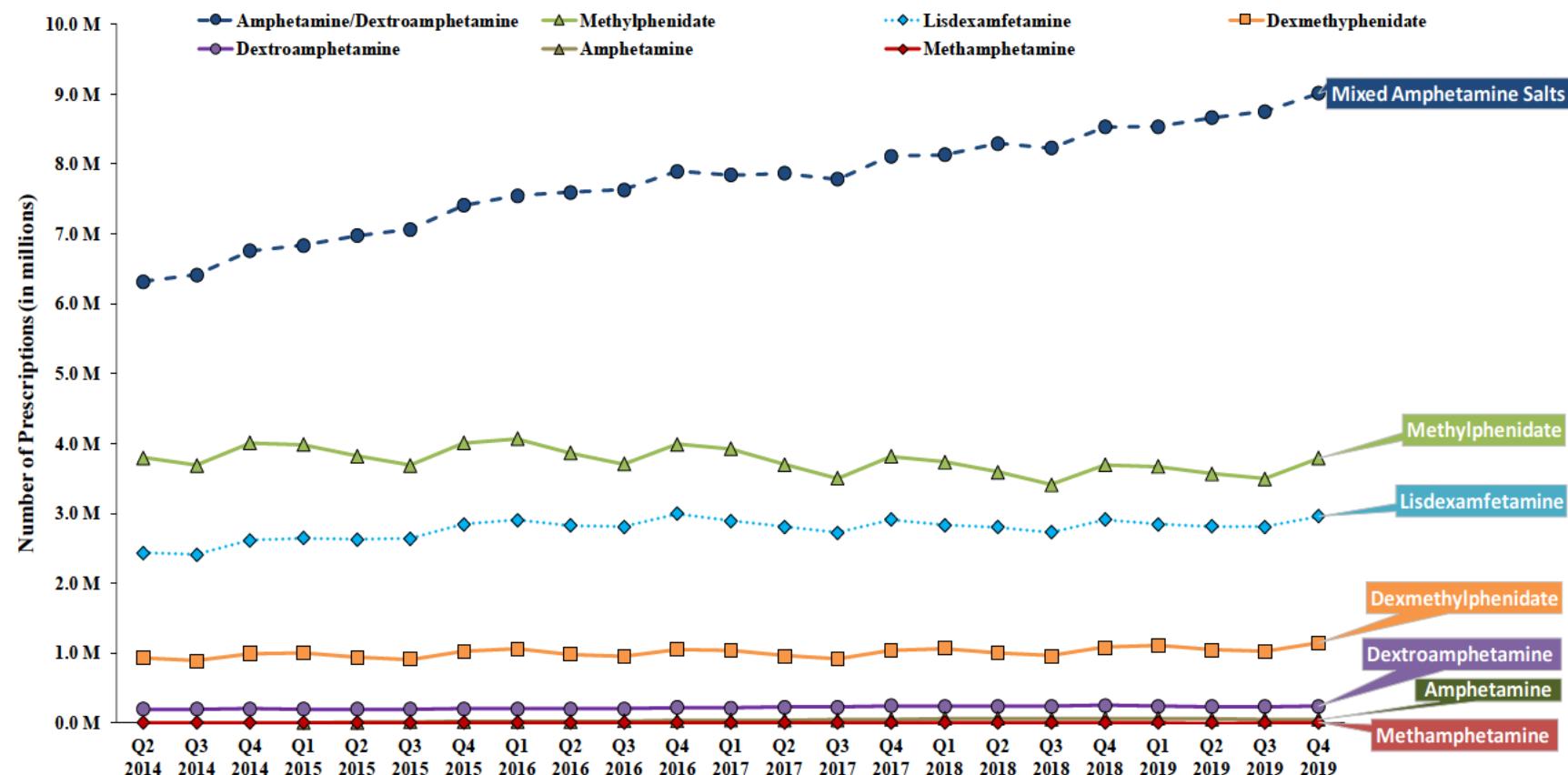


CII, Schedule II; ER, extended-release; IR, immediate-release; U.S., United States.

Source: FDA analysis of IQVIA, National Prescription Audit™. 2014–2019. Extracted March 2020. File: 2020-95 NPA stimulants TRx IR vs ER NPA Mar-11-2020.xlsx.

Figure 3, below and Table 61 in Section 4.2 shows the nationally estimated number of prescriptions dispensed for CII stimulants by drug from U.S. outpatient retail pharmacies from the second quarter of 2014 through the fourth quarter of 2019. While the use of other CII stimulants remained steady, mixed amphetamine salts, which include a mixture of salts containing amphetamine and dextroamphetamine, increased 43% from approximately 6.3 million prescriptions to 9 million prescriptions, largely driving the overall increase from 2014 through 2019. Of the estimated 17 million prescriptions dispensed for CII stimulants in the fourth quarter of 2019, racemic amphetamine sulfate accounted for 0.3% (approximately 53,000 prescriptions) of the overall stimulant market and has remained steady throughout the study-period.

Figure 3. National estimates of prescriptions dispensed for CII stimulants, stratified by drug, from U.S. outpatient retail pharmacies from the second quarter of 2014 through the fourth quarter of 2019

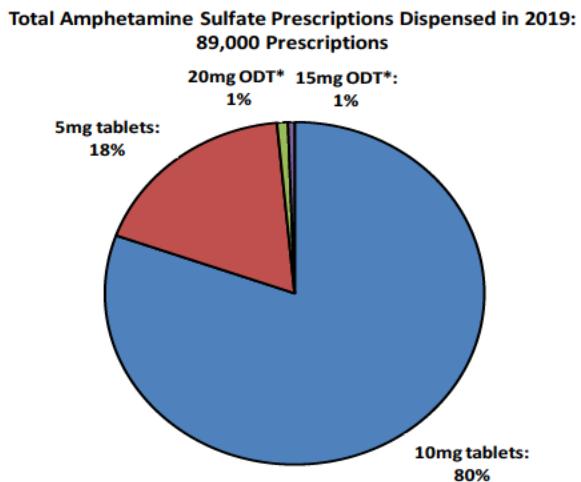


CII, Schedule II; U.S., United States.

Source: FDA analysis of IQVIA, National Prescription Audit™. 2014–2019. Extracted March 2020. File: 2020-95 NPA stimulants TRx molecule_1_Mar-09-2020.xlsx.

To create context for the applicant's proposed abuse-deterrent formulation of an IR racemic amphetamine tablet, the top strengths for IR racemic amphetamine prescriptions were assessed. In 2019, 10mg followed by 5mg strength accounted for nearly 98% of the IR racemic amphetamine tablets dispensed (Figure 4 and Table 62 in Section 4.2).

Figure 4. National estimates of prescriptions dispensed for IR racemic amphetamine sulfate, stratified by drug strength, from U.S. outpatient retail pharmacies, in 2019



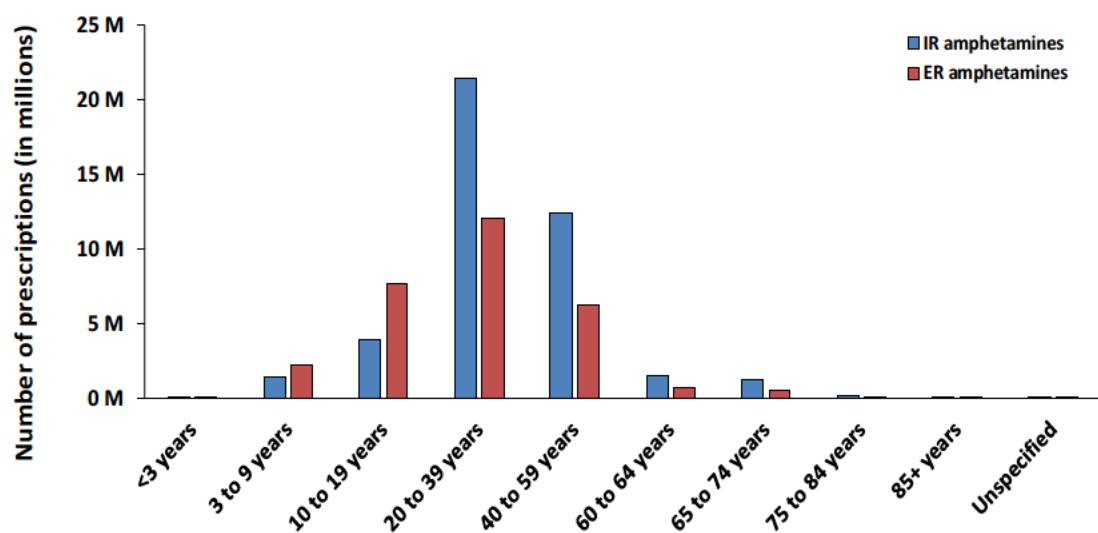
IR, immediate-release; U.S., United States.

Note: '*' ODT: orally disintegrating tablet.

Source: FDA analysis of IQVIA, National Prescription Audit™. 2019. Extracted July 2020. File: 2020-95 NPA racemic amphetamine strength 2019.xlsx.

Figure 5 and Table 63 in Section 4.2 show national estimates of prescriptions for IR amphetamines compared to ER amphetamines, stratified by patient age, from U.S. outpatient retail pharmacies from January 2018 through December 2019. During these two years, IR amphetamine use was higher in patients aged 20 years and older, while ER amphetamine use was higher in patients aged 19 years and younger. Patients 20 to 39 years old were dispensed almost twice as many prescriptions for IR formulations as ER formulations.

Figure 5. National estimates of prescriptions dispensed for *IR amphetamines* or *ER amphetamines*, stratified by patient age, from U.S. outpatient retail pharmacies, January 2018 through December 2019



Source: IQVIA, National Prescription Audit™. 2018-2019. Extracted: July 2020.

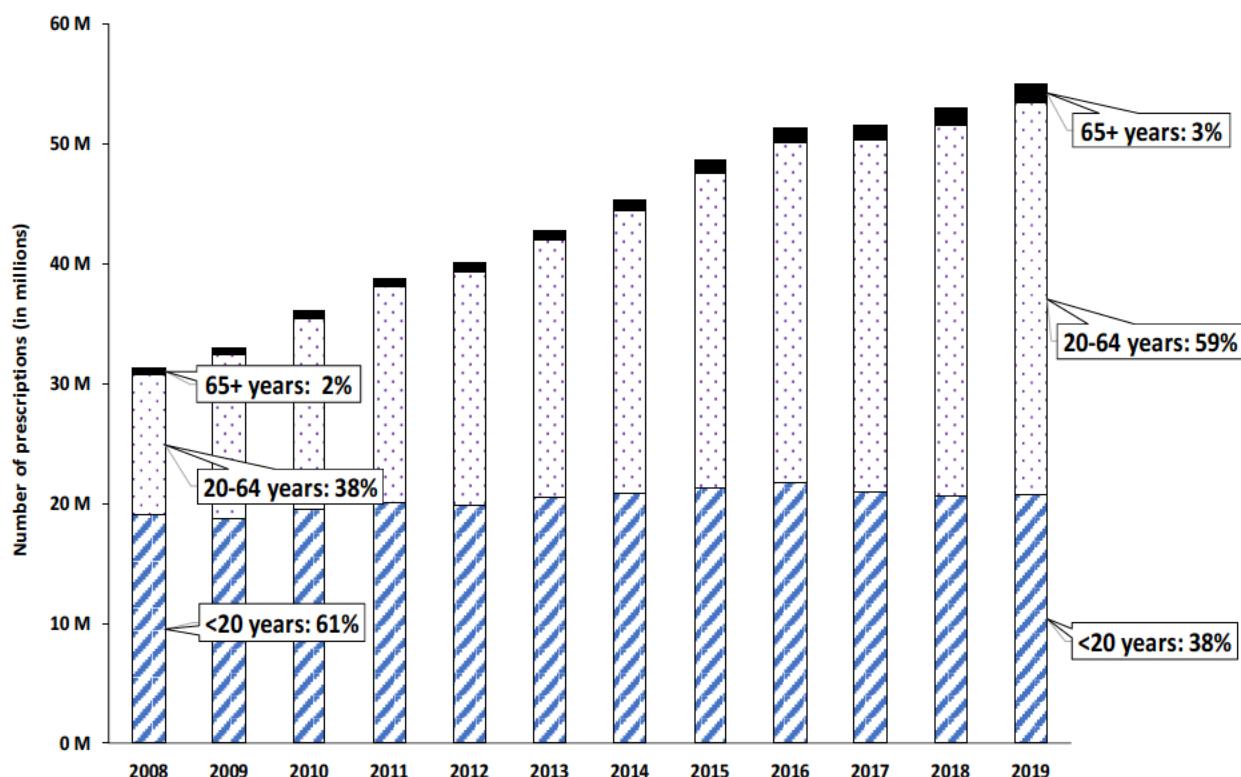
*Amphetamines include amphetamine mixed salts, amphetamines, and dextroamphetamine

ER, extended-release; IR, immediate-release; U.S., United States.

Source: FDA analysis of IQVIA, National Prescription Audit™. 2018-2019. Extracted July 2020. File: 2020-95 NPA amphetamine ir vs er by age Jul-09.xlsx.

Figure 6 and Table 64 in Section 4.2 displays the national estimates of prescriptions dispensed for CII stimulants, stratified by patient age (<20 years, 20-64 years, and 65+ years), from 2008-2019, yearly. Overall, prescriptions received by patients of all ages increased in the 11-year span. Prescriptions dispensed to patients aged 20-64 years accounted for the largest increase, from approximately 38% (11.8 million prescriptions) of total prescriptions in 2008 to 59% (32.7 million prescriptions) in 2019.

Figure 6. National estimates of prescriptions dispensed for CII stimulants, stratified by patient age (<20 years, 20-64 years, and 65+ years), from U.S. outpatient retail pharmacies, January 2008 through December 2019



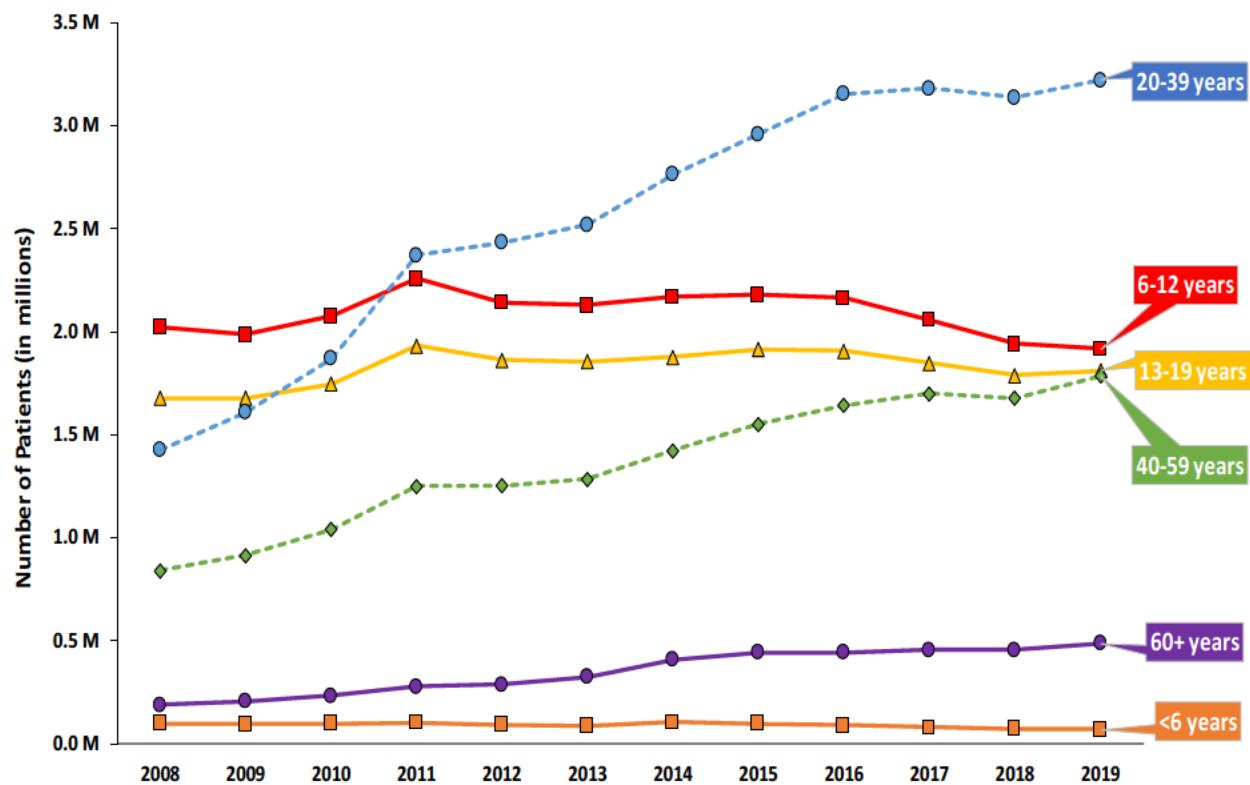
CII, Schedule II; U.S., United States.

Source: FDA analysis of IQVIA, National Prescription Audit™. 2008-2019. Extracted April 2020. File: 2020-95 NPA stimulants by age Apr-2020.xlsx.

3.1.3 Patient Data from U.S. Outpatient Retail Pharmacies

Figure 7 and Table 65 in Section 4.2 show the national estimates of patients who received dispensed prescriptions for CII stimulant products, stratified by patient age (<6 years, 6-12 years, 13-19 years, 20-39 years, 40-59 years, 60+ years), from 2008 through 2019, yearly. The total number of patients who received dispensed prescriptions for CII stimulants increased 45% from an estimated 6.3 million patients in 2008 to 9.2 million patients in 2019. Patients aged 20-39 years and 40-59 years accounted for the largest increases, increasing 126% and 113% from 1.4 million patients and 840,000 patients in 2008 to 3.2 million patients and 1.8 million in 2019, respectively. In 2019, CII prescription stimulant products were most frequently dispensed to patients 20 to 39 years old, followed by patients 6 to 12 years old and patients 13 to 19 years old.

Figure 7. National estimates of patients who received dispensed prescriptions for CII stimulants, stratified by patient age (<6 years, 6-12 years, 13-19 years, 20-39 years, 40-59 years, 60+ years), from U.S. outpatient retail pharmacies, January 2008 to December 2019



Note: Patient age subtotals may not sum exactly due to patients aging during the study period and may be counted more than once in the individual age categories. For this reason, summing across time periods or patient age bands is not advisable and will result in overestimates of patient counts.

Source: FDA analysis of IQVIA, Total Patient Tracker™. 2008-2019. Extracted March 2020. File: 2020-95 TPT Stimulant group 2008-2019 report.xlsx.

3.1.4 Survey Data from Office-Based Physicians

An analysis of the top diagnoses associated with the use of CII stimulant products as reported by U.S. office-based physician surveys was conducted for two 24-month time-periods, from January 2011 through December 2012 and from January 2018 through December 2019 (**Table 8**). From 2011 through 2012, most drug use mentions²³ for CII stimulants were for patients aged 20 years and younger at 57% of total mentions. From 2018 through 2019, the top age group associated with CII stimulant use was 20-64 years old at 53% of total mentions. In both age groups, ADHD was recorded as the top diagnosis in both distinct study time-periods.

²³ The term "drug use mentions" refer to mentions of a drug in association with a diagnosis during a patient visit to an office-based physician. This term may be duplicated by the number of diagnoses for which the drug is mentioned. It is important to note that a "drug use" does not necessarily result in a prescription being generated. Rather, the term indicates that a given drug was mentioned during an office visit.

Table 8. Top diagnoses* associated with the use of CII stimulant products as reported by U.S. office-based physician surveys from January 2011 to December 2012 and January 2018 to December 2019

	January 2011-December 2012			January 2018-December 2019			
	Share (%)	Uses (000)	95% CI (000)	Share (%)	Uses (000)	95% CI (000)	
Total CII Stimulants	100%	32,744	31887-33601	Total CII Stimulants	100%	40,734	39404-42064
<20 years	56.6%	18,520	17875-19165	<20 years	43.7%	17,799	16919-18678
F90 Attention-deficit hyperactivity disorders	96.3%	17,842	17209-18475	F90 Attention-deficit hyperactivity disorders	94.1%	16,741	15888-17594
F91 Conduct disorders	1.1%	212	143-281	Z00 Encntr for general exam w/o complaint	4.3%	772	589-955
F84 Pervasive developmental disorders	1.0%	182	118-245	F50 Eating disorders	0.4%	73	17-130
F81 Specific developmental disorders of scholastic skills	0.2%	44	13-75	R41 Oth symp and signs w/ cognitive func and awareness	0.4%	72	16-128
Z76 Persons encounter health services in oth circumstance	0.2%	33	6-60	F91 Conduct disorders	0.3%	50	3-97
All Others	1.1%	207	139-276	All Others	0.5%	90	28-153
20-64 years	38.3%	12,528	11997-13058	20-64 years	53.0%	21,583	20615-22551
F90 Attention-deficit hyperactivity disorders	93.0%	11,649	11138-12160	F90 Attention-deficit hyperactivity disorders	89.4%	19,286	18371-20202
Z76 Persons encounter health services in oth circumstance	1.6%	195	129-261	F50 Eating disorders	6.3%	1,356	1113-1599
F32 Major depressive disorder, single episode	1.5%	187	122-252	R41 Oth symp and signs w/ cognitive func and awareness	1.4%	296	182-409
F31 Bipolar disorder	0.7%	85	42-129	G47 Sleep disorders	0.7%	151	70-231
G47 Sleep disorders	0.5%	65	27-103	Z00 Encntr for gen exam w/o complaint, susp or reproto dx	0.6%	118	47-190
All Others	2.8%	346	258-434	All Others	1.7%	376	248-504
65+ years	1.1%	366	276-457	65+ years	1.6%	655	487-824
F90 Attention-deficit hyperactivity disorders	60.6%	222	151-292	F90 Attention-deficit hyperactivity disorders	81.2%	533	380-685
F32 Major depressive disorder, single episode	21.0%	77	35-119	F34 Persistent mood [affective] disorders	6.5%	43	<0.5-86
F34 Persistent mood [affective] disorders	5.0%	18	<0.5-38	G35 Multiple sclerosis	3.5%	23	<0.5-55
F43 Reaction to severe stress, and adjustment disorders	2.5%	9	<0.5-23	F32 Major depressive disorder, single episode	3.0%	19	<0.5-48
F20 Schizophrenia	1.8%	7	<0.5-19	R60 Edema, not elsewhere classified	2.4%	16	<0.5-42
All Others	9.2%	34	6-61	All Others	3.4%	22	<0.5-53
Unspecified age	4.1%	1,330	1158-1503	Unspecified age	1.7%	697	523-871

CII, Schedule II; ICD-10, International Classification of Diseases, Tenth Revision; U.S., United States.

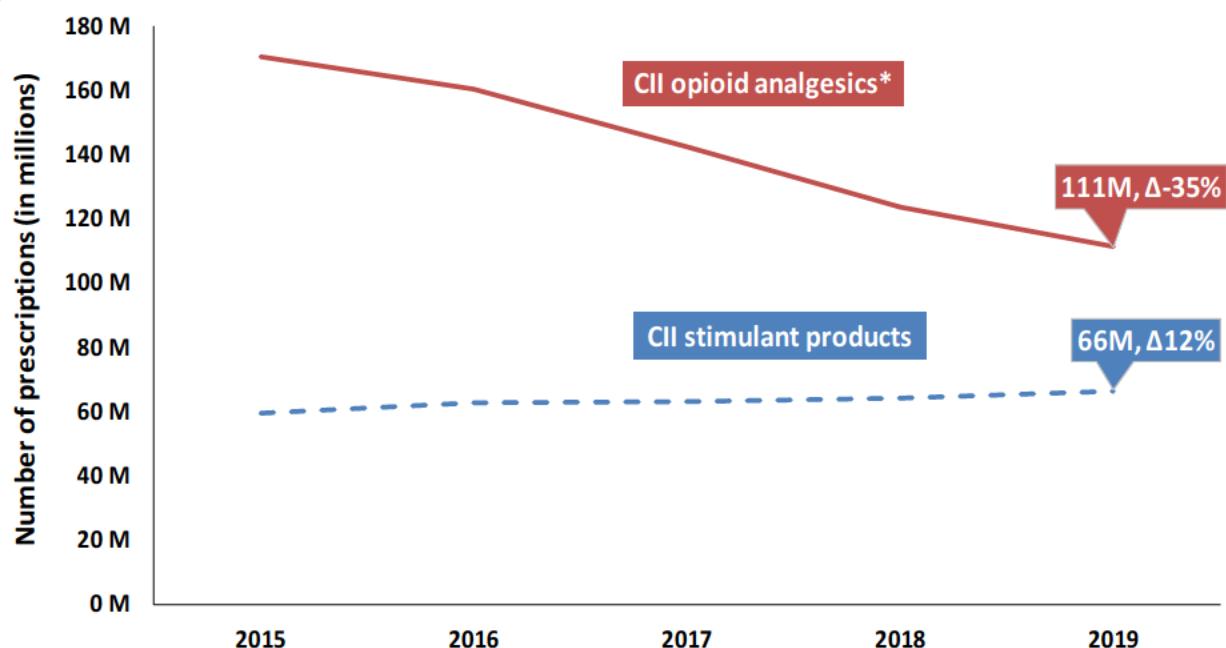
Note: '*' indicates that diagnoses are expressed as "drug use mentions" which refers to mentions of a drug in association with a diagnosis during a patient visit to an office-based physician. This term may be duplicated by the number of diagnosis for which the drug is mentioned. It is important to note that a "drug use" does not necessarily result in prescription being generated. Rather, the term indicates that a given drug was mentioned during an office visit. Diagnoses are based on ICD-10.

Source: FDA analysis of Syneos Health, Treatment Answers™. 2011-2019. Data extracted April 2020. File: 2020-95 Syneos Stimulants top 5 diagnoses 2011-2019.xls.

3.1.5 Comparison of Opioid and Stimulant Prescription Data

Figure 8 and Table 66 in Section 4.2 display national estimates of prescriptions for opioid analgesics compared to CII stimulant products dispensed annually from U.S. outpatient retail pharmacies from 2015 through 2019. The number of opioid analgesic prescriptions dispensed decreased 35% from approximately 170 million prescriptions in 2015 to 111 million prescriptions in 2019, while CII stimulant product prescriptions increased 12% from 60 million to 66 million prescriptions during the same time-period. The number of prescriptions dispensed for opioid analgesics was approximately three times that of CII stimulant products in 2015 and slightly decreased to approximately two times the number of dispensed CII stimulant products in 2019.

Figure 8. National estimates of prescriptions dispensed for CII opioid analgesics or CII stimulant products, from U.S. outpatient retail pharmacies, January 2015 through December 2019



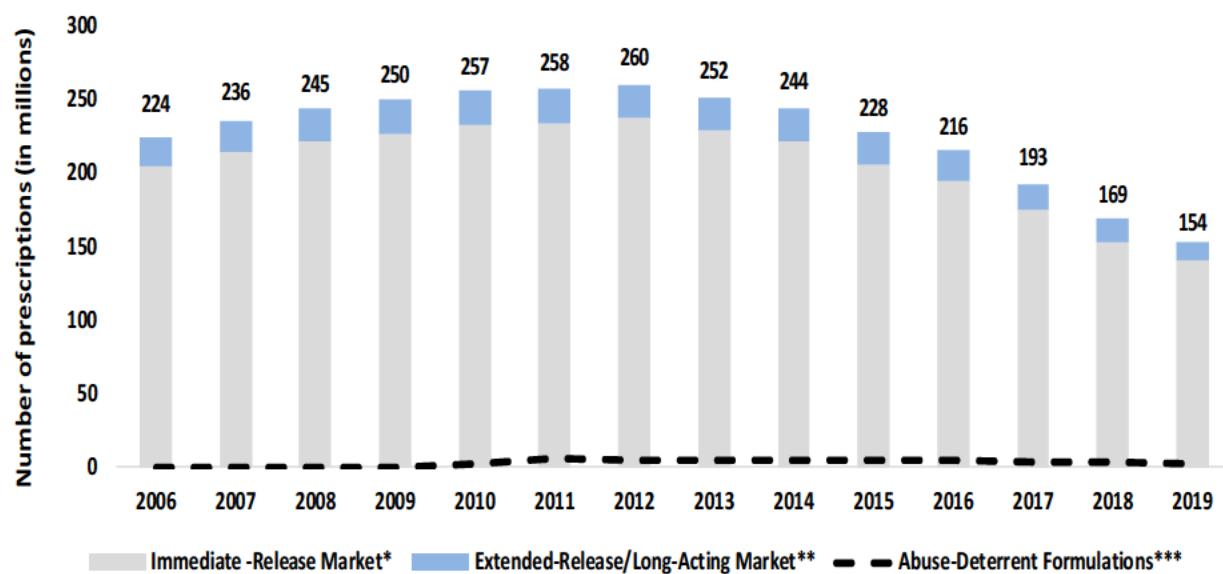
CII, Schedule II; U.S., United States.

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

Source: FDA analysis of IQVIA, National Prescription Audit™. 2019. Extracted July 2020. File: 2020-95 NPA stimulants vs opioids.xlsx.

Figure 9 and Table 67 in Section 4.2 shows the estimated number of prescriptions dispensed for all opioid analgesics regardless of CSA schedule (single and combination products), stratified by formulation (immediate-release, extended-release, and abuse-deterrent) from U.S. outpatient retail pharmacies from January 2006 through December 2019. IR formulations accounted for 91% (141 million prescriptions) of the total opioid analgesic prescriptions dispensed in 2019, followed by extended-release/long-acting formulations at 9% (13 million prescriptions), and abuse-deterrent formulations at 1.7% (2.7 million prescriptions).

Figure 9. Nationally estimated number of prescriptions dispensed for opioid analgesic products (all CSA schedules), stratified by formulation, from U.S. outpatient retail pharmacies, January 2006 through December 2019



CSA, Controlled Substance Act; IR, immediate-release; ER, extended-release; U.S., United States.

Note: ** indicates Immediate-Release formulations that include oral solids, oral liquids, rectal, nasal, and transmucosal formulations.

Note: *** indicates Extended-Release/Long-Acting formulations that include oral solids and transdermal patches.

Note: **** indicates abuse-deterrent formulation opioid products that include Arymo ER, Embeda ER, Hysingla ER, Morphabond ER, Xtampza ER, OxyContin ER Reformulated (Approval in April 2010), RoxyBond IR.

Note: These data include non-injectable opioid analgesics only. Opioid-containing cough-cold products and opioid-containing medication-assisted treatment (MAT) products are not included.

Source: FDA analysis of IQVIA, National Prescription Audit (NPA) and static data 2006-2011. January 2006-December 2019. Static data extracted March 2017, 2012-2017 data extracted February 2018, 2018 data extracted March 2019, 2019 data extracted Jan 24, 2020.

File: 2020-95 NPA Opioid Slide Deck ALL for ADFs Total IR and ER TRx Update for 2019 1-24-2020 (003).xlsx.

3.2 POSTMARKETING DATA ON NMU AND RELATED OUTCOMES INVOLVING CII STIMULANTS

3.2.1 Scale of NMU of Prescription Stimulants

3.2.1.1 General U.S. Population Studies

Prevalence of Prescription Stimulant NMU in the General Population

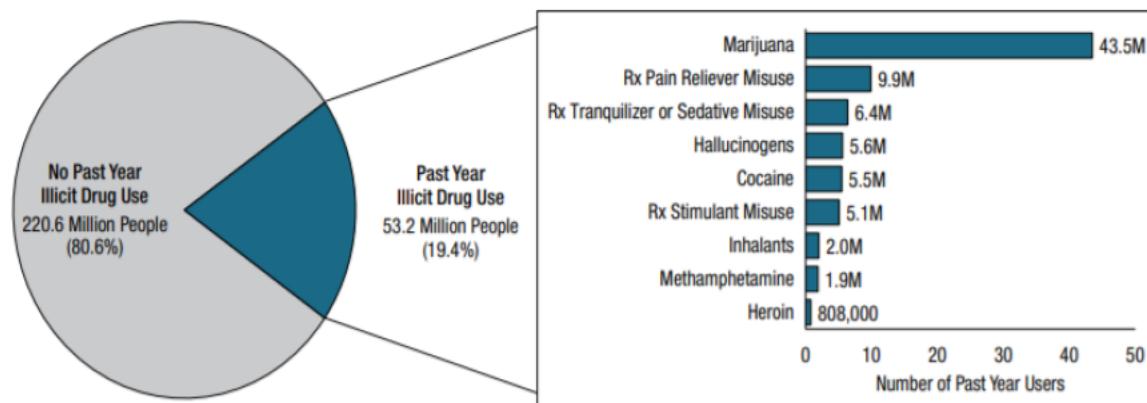
Data from the most recent available year of NSDUH (2018) estimated 53.2 million people aged 12 years or older used an illicit drug²⁴ in the past year, corresponding to approximately 19.4% of the population (Figure 10). Marijuana was the most common illicit drug, with use by an estimated 43.5 million people, followed by prescription pain relievers,²⁵ with NMU by an estimated 9.9 million people.

In 2018, results from NSDUH also estimated 5.1 million people aged 12 years or older used prescription stimulants nonmedically in the past year, corresponding to approximately 1.9% of the population (Figure 10). In the Applicant-submitted general population online survey (AR19.MA004), 2.8% of respondents aged 18 to 49 years reported NMU of prescription stimulants in the past year (Figure 11).

²⁴ NSDUH defines illicit drugs as marijuana, cocaine (including crack), heroin, hallucinogens, inhalants, methamphetamine, or prescription psychotherapeutics that were misused, which include pain relievers, tranquilizers, stimulants, and sedatives.

²⁵ In NSDUH, pain relievers are largely comprised of prescription opioid analgesics.

Figure 10. Past-year illicit drug use among people aged 12 years or older, National Survey on Drug Use and Health, 2018



Rx, prescription.

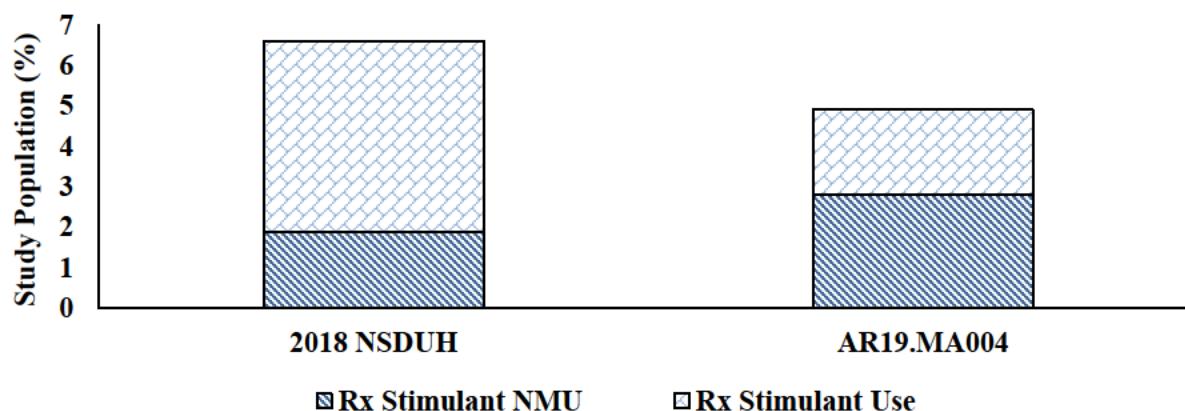
Note: The estimated numbers of past year users of different illicit drugs are not mutually exclusive because people could have used more than one type of illicit drug in the past year.

Note: Illicit drug use included use of marijuana, cocaine (including crack), heroin, hallucinogens, inhalants, methamphetamine, or misuse of prescription (e.g., pain relievers, tranquilizers, stimulants, and sedatives).

Note: Misuse (i.e., nonmedical use) of prescription drugs is defined as use in any way not directed by a doctor, including use without a prescription of one's own; use in greater amounts, more often, or longer than told; or use in any other way not directed by a doctor.

Source: Center for Behavioral Health Statistics and Quality. Results from the National Survey on Drug Use and Health, 2018. Retrieved from <https://www.samhsa.gov/data/>.

Figure 11. Past-year prescription stimulant use and NMU, National Survey on Drug Use and Health and AR19.MA004, an online survey of the general U.S. population conducted by the internet panel company YouGov



NMU, nonmedical use; NSDUH, National Survey on Drug Use and Health; Rx, prescription; U.S., United States.

Note: In NSDUH, NMU is defined as *misuse*, which is use in any way not directed by a doctor, including use without a prescription of one's own; use in greater amounts, more often, or longer than told to take a drug; or use in any other way not directed by a doctor.

Note: In AR19.MA004, NMU is defined as use for any reason, even once, without your own prescription; Use in ways other than prescribed (such as taking more than prescribed, more often than prescribed, or for any other reason/way than prescribed; Use for the feeling or experience the medication caused (such as feeling of being high, enhancement of other drugs, prevention or treatment of withdrawal symptoms or other feelings).

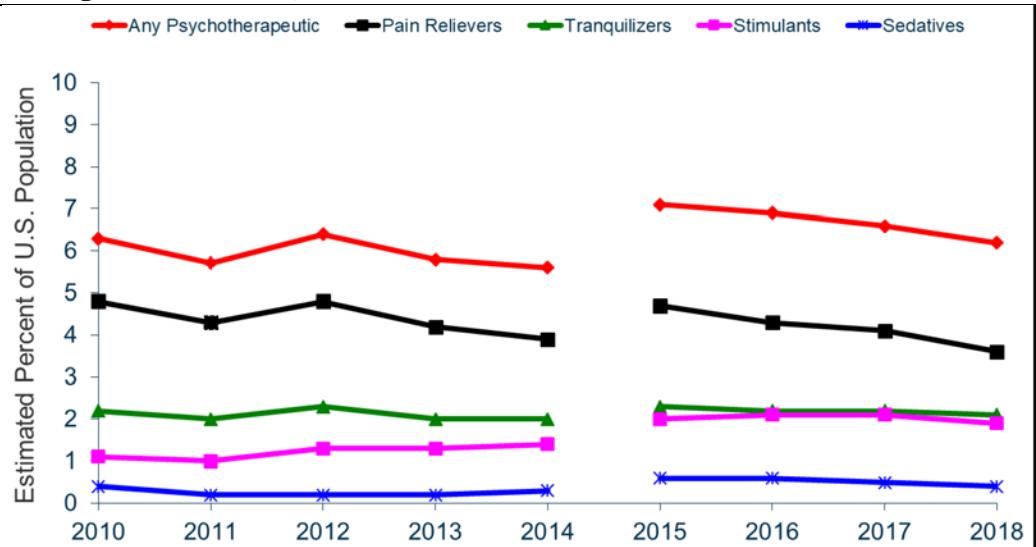
Note: NSDUH includes people aged 12 years and older. AR19.MA004 includes people aged 18 to 49 years.

Source(s): FDA-generated figure. (1) Data from the Center for Behavioral Health Statistics and Quality. The National Survey on Drug Use and Health, 2018. Retrieved from <https://www.samhsa.gov/data/>. (2) Nonmedical Use of Prescription Medications among the General Population (AR19.MA004). Results from Table 3. Lifetime use of prescription medications (with and without own prescription, for any reason) and Table 7. Lifetime use and NMU of prescription medications.

In NSDUH, the prevalence of past-year prescription stimulant NMU was stable from 2010 through 2014 and from 2015 through 2018, whereas the prevalence of past-year prescription pain reliever misuse

decreased slightly but remained greater than stimulant NMU across both time periods (**Figure 12**). It is important to note that NSDUH was redesigned in 2015, creating a trend break between 2014 and 2015 that limits analyses of trends in NSDUH; however, there is no indication of meaningful changes in the estimates across either the 2010 through 2014 or 2015 through 2018 time periods.

Figure 12. Past-year NMU of psychotherapeutics among people aged 12 years or older, National Survey on Drug Use and Health, 2010 to 2018



NMU, nonmedical use.

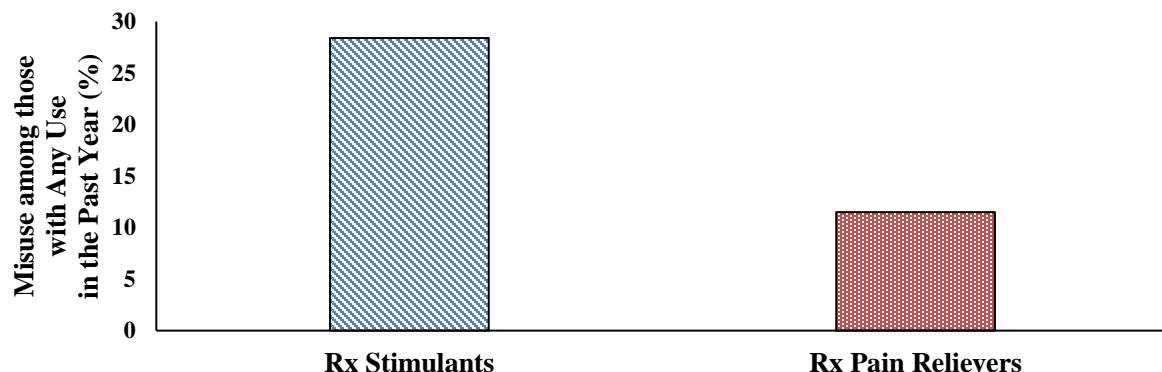
Note: Misuse (i.e., NMU) of psychotherapeutics is defined as use in any way not directed by a doctor, including use without a prescription of one's own; use in greater amounts, more often, or longer than told to take a drug; or use in any other way not directed by a doctor.

Note: NSDUH was redesigned in 2015, creating a trend break between 2014 and 2015.

Source: Figure 3 from Pinney Associates Report Prepared for Arbor Pharmaceuticals, LLC: Public Health Rationale for AR-19 (Amphetamine Sulfate Immediate Release Abuse Deterrent) Capsules (AR19.MA011).

Although data collected from NSDUH in 2018 suggested NMU of prescription stimulants is not as common in the general population as NMU of prescription pain relievers, as shown in **Figure 10, above** (5.1 vs. 9.9 million people), **Figure 13** shows that the proportion reporting NMU in the past year among those reporting any use was greater for prescription stimulants (28.4%) as compared to prescription pain relievers (11.5%).

Figure 13. Past-year NMU among people aged 12 years or older with any use, National Survey on Drug Use and Health, 2018



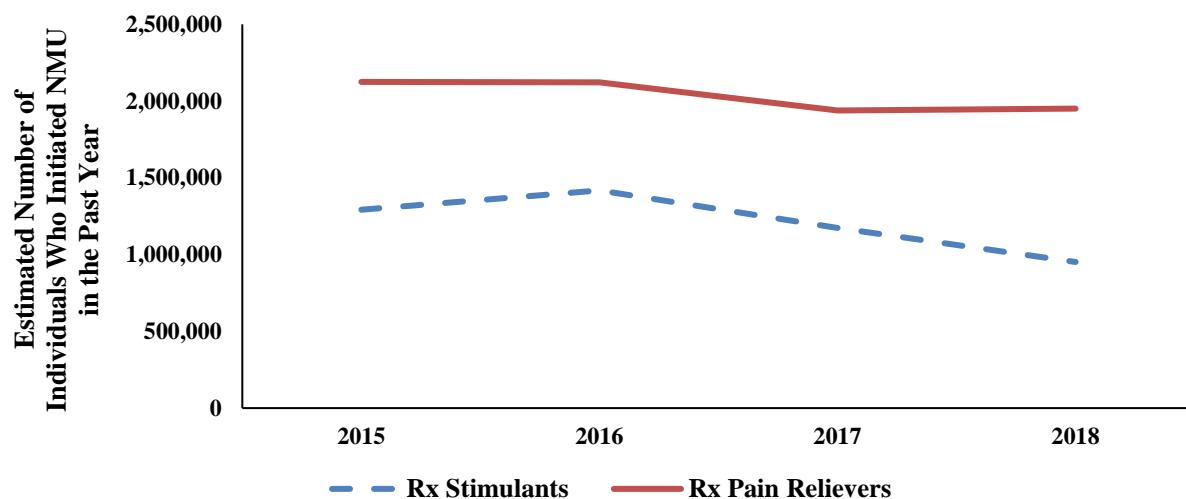
NMU, nonmedical use; Rx, prescription.

Note: Misuse (i.e., NMU) of psychotherapeutics is defined as use in any way not directed by a doctor, including use without a prescription of one's own; use in greater amounts, more often, or longer than told to take a drug; or use in any other way not directed by a doctor.

Source: FDA-generated figure. Center for Behavioral Health Statistics and Quality. Results from the National Survey on Drug Use and Health, 2018. Retrieved from <https://www.samhsa.gov/data/>.

Despite a relatively consistent level of prescription stimulant NMU observed between 2015 and 2018 among adults aged 12 years or older in NSDUH, the estimated number of people initiating prescription stimulant NMU in the past year across the same time period dropped from approximately 1.3 million people to 0.9 million people (**Figure 14**). For comparison, the percentage of people aged 12 years or older with past year NMU of prescription pain relievers in 2018 was approximately 22% lower than 2015 (**Figure 12, shown previously**), while the number of people aged 12 years or older who initiated any pain reliever NMU in the past year dropped slightly between 2015 and 2018 from approximately 2.1 million people to 1.9 million people (**Figure 14**).

Figure 14. Past-year initiation of NMU of prescription stimulants and pain relievers, among people aged 12 years or older, National Survey on Drug Use and Health, 2015 to 2018



NMU, nonmedical use; Rx, prescription.

Note: NMU of psychotherapeutics is defined as use in any way not directed by a doctor, including use without a prescription of one's own; use in greater amounts, more often, or longer than told to take a drug; or use in any other way not directed by a doctor.

Source: FDA-generated figure. Center for Behavioral Health Statistics and Quality. Results from the National Survey on Drug Use and Health, 2018. Retrieved using the crosstab analyses tool made available by the Public-use Data Analysis System provided by SAMHSA. Available at: <https://www.samhsa.gov/data/>.

Self-reported Use and NMU of Prescription Stimulants by API

Table 9 describes data collected from NSDUH (2018) on the past-year use and NMU among people aged 12 years or older, by type of prescription stimulant. The most common prescription stimulants used and nonmedically used in the past year were amphetamine products (4.5% and 1.7%, respectively), followed by methylphenidate products (1.1% and 0.3%, respectively). Only a small percentage of prescription stimulant use and NMU was comprised of drugs other than these CII prescription stimulant APIs. The percentages of individuals reporting any past-year amphetamine and methylphenidate use who also reported NMU of these products were 37.8% and 23.8%, respectively.

Table 9. Past-year prescription stimulant use and NMU among people aged 12 years or older, by stimulant subtype, National Survey on Drug Use and Health, 2018

Stimulant Subtype	Any Use in Past Year (%)	NMU in Past Year (%)	NMU in the Past Year Among Any Use (%)
Amphetamine Products	4.5	1.7	37.8
Methylphenidate Products	1.1	0.3	23.8
Anorectic (Weight-Loss) Stimulants	0.9	0.1	5.9
Provigil®	0.2	0.0	*
Any Other Prescription Stimulant	1.0	0.0	3.2

NMU, nonmedical use.

Note: ** indicates low precision.

Note: Any use of prescription psychotherapeutics is defined as (a) the use of one's own prescription medication as directed by a doctor or (b) misuse (i.e., NMU) of prescription psychotherapeutics. Misuse of prescription psychotherapeutics is defined as use in any way not directed by a doctor, including use without a prescription of one's own; use in greater amounts, more often, or longer than told; or use in any other way not directed by a doctor. Prescription psychotherapeutics do not include over-the-counter drugs.

Note: Anorectic (Weight-Loss) Stimulants include Didrex®, benzphetamine, Tenuate®, diethylpropion, phendimetrazine, and phentermine.

Note: Any Other Prescription Stimulant category includes use or misuse of stimulants containing other active ingredients. Reports of misuse of "any other prescription stimulant" that correspond only to the specific stimulant categories shown in the table are excluded from estimates for Any Other Prescription Stimulant and are included instead in the relevant stimulant category.

Source: Center for Behavioral Health Statistics and Quality. Results from the National Survey on Drug Use and Health, 2018. Retrieved from <https://www.samhsa.gov/data/>.

Table 10 summarizes data on lifetime use of selected prescription stimulant brands reported by respondents of the Applicant-submitted general population survey, AR19.MA004, with a history of NMU of prescription stimulants. Among those respondents who reported NMU of prescription stimulants, lifetime *use* of amphetamine brands was more common than methylphenidate brands (76.8% and 43.0%, respectively). The most common prescription amphetamine brands ever used were Adderall (76.8%) and Adderall XR (52.2%), while the most common prescription methylphenidate brands ever used were Ritalin (20.6%) and Concerta (14.8%).

Table 10. Lifetime use of prescription stimulants among respondents with a history of NMU of prescription stimulants, by stimulant brand, AR19.MA004, an online survey of the general U.S. population conducted by the internet panel company YouGov

Brand	Lifetime Use among Prescription Stimulant Nonmedical Users (N=762)	
	n	%
Any amphetamine	585	76.8
Adderall	398	52.2
Adderall XR	268	35.2
Dexedrine	32	4.2
Dexedrine spansules	40	5.3
Dextrostat	39	5.1
Desoxyn	18	2.4
Vyvanse	133	17.5
Any methylphenidate	328	43.0
Concerta	113	14.8
Metadate CD	33	4.3
Metadate ER	26	3.4
Methylin	16	2.1
Methylin ER	18	2.4
Ritalin	157	20.6
Ritalin LA	49	6.4
Ritalin SR	49	6.4
Daytrana	19	2.5
Focalin	17	2.2
Focalin XR	25	3.3
Other prescription stimulant	108	14.2

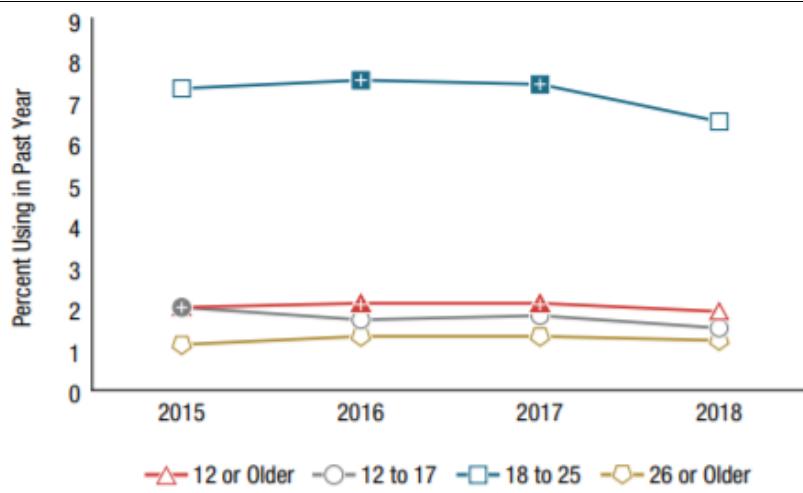
NMU, nonmedical use; U.S., United States.

Source: Nonmedical Use of Prescription Medications among the General Population (AR19.MA004). Results from Table 11. Lifetime history of prescription stimulants used (with or without own prescription) among participants reporting NMU of prescription stimulants.

3.2.1.2 Prevalence of Prescription Stimulant NMU in Young Adults and Adolescents

Data collected from NSDUH between 2015 and 2018 have consistently shown the greatest percentage of prescription stimulant NMU is among people aged 18 to 25 years (**Figure 15**). The most recent data available from NSDUH (2018) showed both use (14.0%) and NMU (7.2%) of prescription stimulants peaked among people aged 21 to 25 years, before steadily declining across older age categories (**Figure 16A**). A similar peak in NMU of prescription pain relievers was observed among people aged 21 to 25 years; however, unlike prescription stimulants, use of prescription pain relievers steadily increased across older age categories (**Figure 16B**).

Figure 15. Past-year prescription stimulant NMU among people aged 12 years or older, by age categories, National Survey on Drug Use and Health, 2015 to 2018



NMU, nonmedical use.

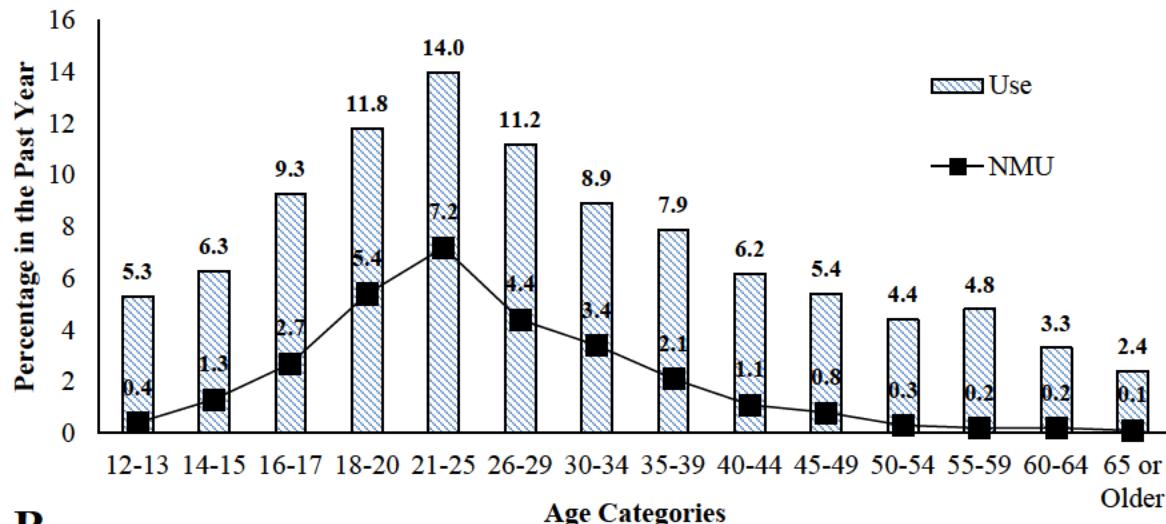
Note: '+' refers to the difference between this estimate and the 2018 estimate is statistically significant at the 0.05 level.

Note: Misuse (i.e., NMU) of prescription drugs is defined as use in any way not directed by a doctor, including use without a prescription of one's own; use in greater amounts, more often, or longer than told; or use in any other way not directed by a doctor.

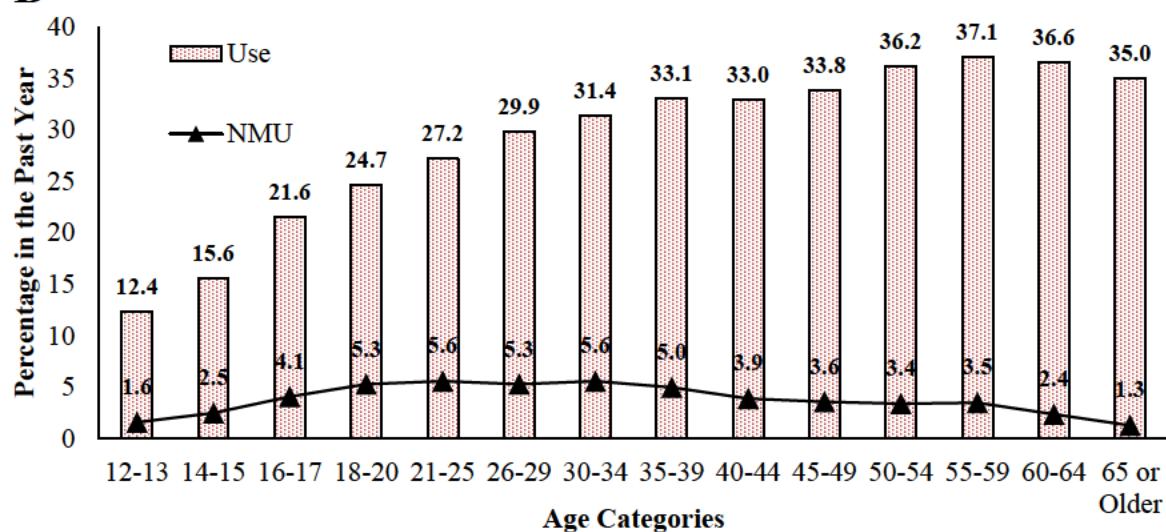
Source: Center for Behavioral Health Statistics and Quality. Results from the National Survey on Drug Use and Health, 2018. Retrieved from <https://www.samhsa.gov/data/>.

Figure 16. Past-year use and NMU of (A) prescription stimulants and (B) prescription pain relievers among people aged 12 years or older, by age categories, National Survey on Drug Use and Health, 2018

A



B



NMU, nonmedical use.

Note: Use of prescription drugs is defined as the use of one's own prescription medication as directed by a doctor or NMU of prescription drugs. Note: NMU of prescription drugs is defined as use in any way not directed by a doctor, including use without a prescription of one's own; use in greater amounts, more often, or longer than told; or use in any other way not directed by a doctor.

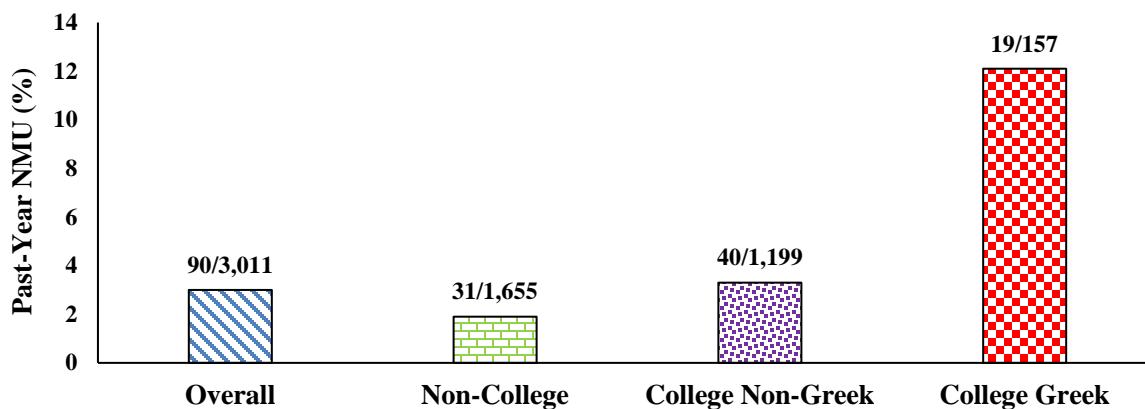
Source: FDA-generated figure. Center for Behavioral Health Statistics and Quality. Results from the National Survey on Drug Use and Health, 2018. Retrieved from <https://www.samhsa.gov/data/>.

Among respondents of the Applicant-submitted online survey AR19.MA012 that were of a similar age range (i.e., 18 to 26 years), 3.0% reported past-year NMU use of prescription stimulants (**Figure 17**). Greater past-year NMU of prescription stimulants was observed among AR19.MA012 respondents enrolled in college (4.4%) compared to those that were not enrolled in college (1.9%). College students who participated in Greek life²⁶ were 3.6 times as likely to report past-year NMU of prescription

²⁶ Greek life refers to respondents enrolled in college that also participate in fraternities and sororities.

stimulants as compared to college students that did not participate in Greek life. An analysis of the MTF sample of 12 graders, full-time college students, and others during one to four years beyond high school that was provided in the AR19.MA011 report noted a similar pattern of higher prevalence of NMU of stimulants among those enrolled full-time in college than those of a similar age who were not full-time college students (**Figure 18**).

Figure 17. Past-year prescription stimulant NMU, by college enrollment status, AR19.MA012, an online survey of the general U.S. population aged 18 to 26 years conducted by the internet panel company YouGov



NMU, nonmedical use; U.S., United States.

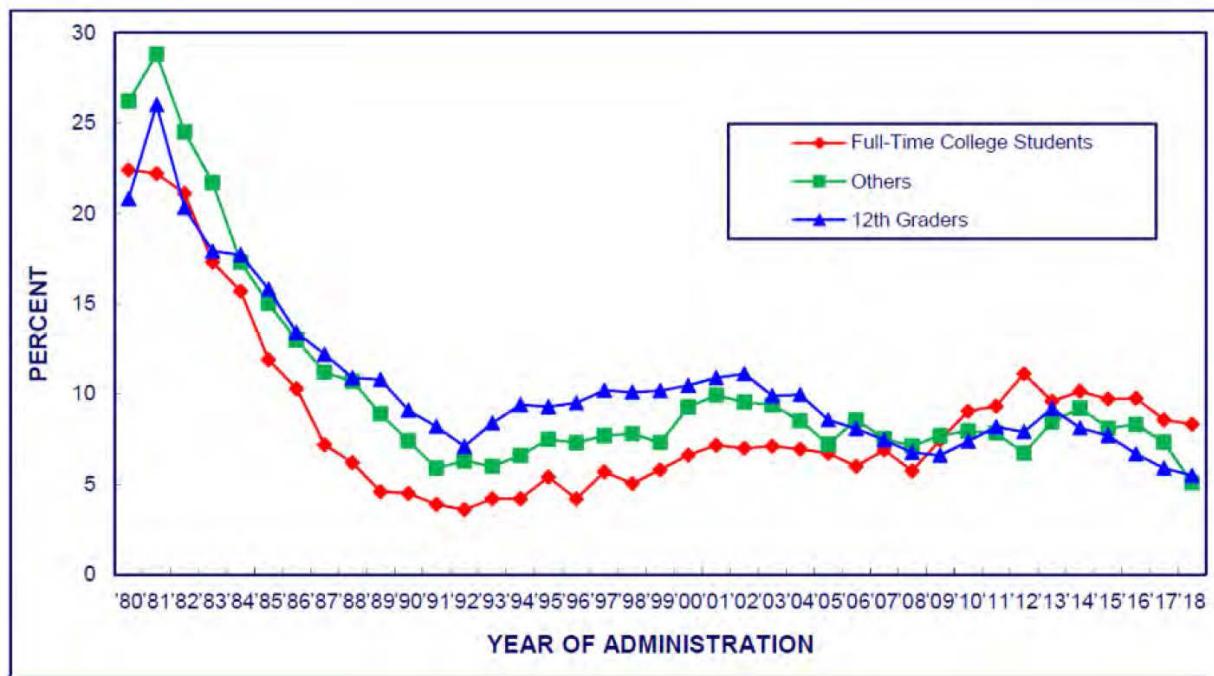
Note: The fractions above each bar represent the number of respondents with NMU of prescription stimulants over the total number of respondents in each category.

Note: Greek refers to participation in fraternities or sororities.

Note: NMU is defined as use for any reason, even once, without your own prescription; Use in ways other than prescribed (such as taking more than prescribed, more often than prescribed, or for any other reason/way than prescribed; Use for the feeling or experience the medication caused (such as feeling of being high, enhancement of other drugs, prevention or treatment of withdrawal symptoms or other feelings).

Source: FDA-generated figure. Nonmedical Use of Prescription Medications in College Students Involved in Greek Life (AR19.MA012). Results from Table 5. Lifetime use and NMU of prescription medications among 18 to 26-year-olds, by enrollment in college and Greek life participation.

Figure 18. Trends in annual prevalence of NMU of amphetamines among college students vs. others one to four years beyond high school with 12th graders for comparison, Monitoring the Future, 1980 to 2018



NMU, nonmedical use.

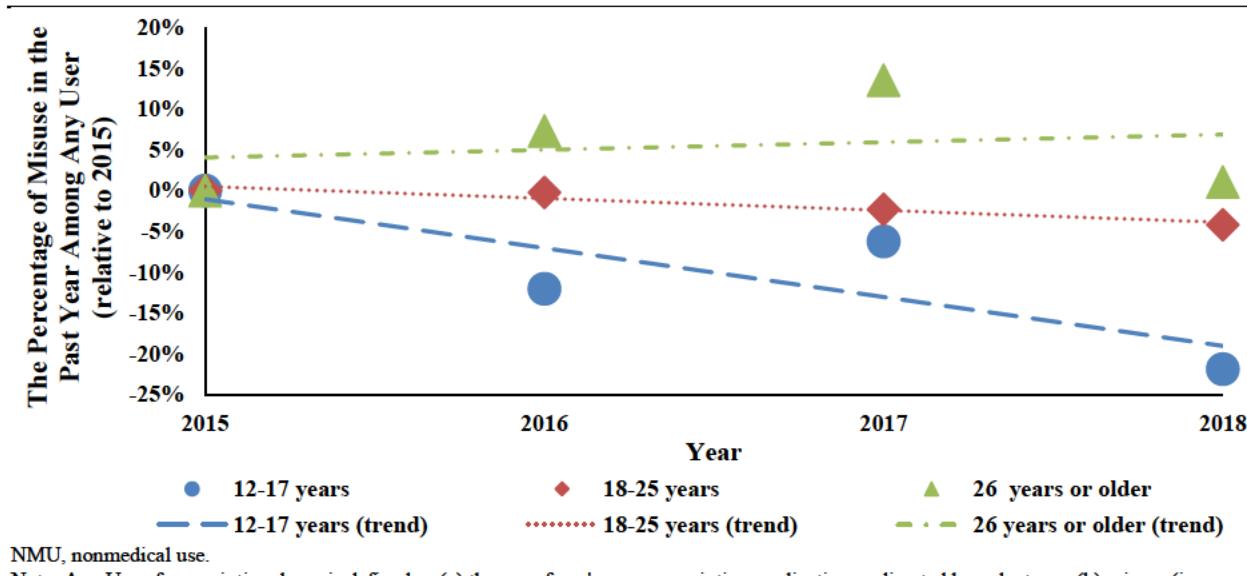
Note: Monitoring the Future follows high school graduates into adulthood. "Others" are peers of college students who are not attending college.

Note: Questionnaire about amphetamines/stimulants was changed starting in 2013 and contains multiple stimulant drug terms such as uppers, ups, speed, bennies, dexies, pep pills, diet pills, meth, crystal meth, Benzedrine, Dexedrine, Methedrine, Ritalin, Adderall, Concerta, and methamphetamine.

Source: Pinney Associates Report Prepared for Arbor Pharmaceuticals, LLC: Public Health Rationale for AR-19 (Amphetamine Sulfate Immediate Release Abuse Deterrent) Capsules (AR19.MA011). Results found in Figure 8.

Unique patterns of use and NMU of prescription stimulants have been observed among young adults. Data collected from NSDUH (2018) estimated 7.0% of people aged 12 to 17 years have used and 1.5% have nonmedically used a prescription stimulant in the past year (**Figure 16A, previously shown**). However, since 2015, people aged 12 to 17 years have also had the greatest reduction in the proportion of individuals with NMU of prescription stimulants among those with any use in the past year, compared to other age categories (e.g., those aged 0 to 25 years and those aged 26 or older) (**Figure 19**). A similar reduction in the prevalence of prescription stimulant NMU has been observed among adolescents enrolled in the eighth, tenth, and twelfth grades as part of the MTF survey, where the annual prevalence of NMU of amphetamines has steadily dropped between 2013 and 2019, from 7.0% to 4.6% (**Table 11**). As a comparison, data collected from MTF between 2013 and 2019 suggested annual prevalence of alcohol use dropped from 42.8% to 35.9%, while the annual prevalence of marijuana use remained constant at approximately 25%.

Figure 19. The percent change in past-year NMU of prescription stimulants among those with any use for people aged 12 years or older, by age categories, National Survey on Drug Use and Health, 2015 to 2018



NMU, nonmedical use.

Note: Any Use of prescription drugs is defined as (a) the use of one's own prescription medication as directed by a doctor or (b) misuse (i.e., NMU) of prescription drugs. Misuse of prescription drugs is defined as use in any way not directed by a doctor, including use without a prescription of one's own; use in greater amounts, more often, or longer than told; or use in any other way not directed by a doctor.

Source: FDA-generated figure. Center for Behavioral Health Statistics and Quality. Results from the National Survey on Drug Use and Health, 2015–2018. Retrieved from <https://www.samhsa.gov/data/>.

Table 11. Trends in annual prevalence of NMU of various selected substances for Grades 8, 10, and 12 combined, Monitoring the Future, 2013 to 2019²⁷

Selected Substances	2013	2014	2015	2016	2017	2018	2019
Alcohol	42.8	40.7	39.9	36.7	36.7	36.1	35.9
Any Vaping	—	—	—	—	21.5	28.9	31.9
Marijuana/Hashish	25.8	24.2	23.7	22.6	23.9	24.3	25.2
Amphetamines*	7.0	6.6	6.2	5.4	5.0	5.0	4.6
Ritalin	1.7	1.5	1.4	1.1	0.8	0.8	0.9
Adderall	4.4	4.1	4.5	3.9	3.5	3.5	3.1
Methamphetamine	1.0	0.8	0.6	0.5	0.5	0.5	0.5
Tranquilizers	3.3	3.4	3.4	3.5	3.6	3.2	3.1
Cocaine	1.8	1.6	1.7	1.4	1.6	1.5	1.4
Heroin	0.6	0.5	0.4	0.3	0.3	0.3	0.3
OxyContin	2.9	2.4	2.3	2.1	1.9	1.7	1.7
Vicodin	3.7	3.0	2.5	1.8	1.3	1.1	1.0

Note: ‘—’ indicates data not available.

Note: '*' contains multiple stimulant drug terms such as uppers, ups, speed, dexies, pep pills, diet pills, meth or crystal meth. They include the drugs Dexedrine, Ritalin, Adderall, Concerta, Vyvanse, Methamphetamine.

Source: The Monitoring the Future Study, the University of Michigan. Results from Table 2. Trends in Annual Prevalence of Use of Various Drugs for Grades 8, 10, 12 Combined. Available at: <http://www.monitoringthefuture.org/pubs/monographs/mtf-overview2019.pdf> (accessed July 7, 2020).

²⁷ Johnston LD, Miech RA, O’Malley PM, Bachman JG, Schulenberg JE, and Patrick ME. Monitoring the Future national survey results on drug use 1975-2019: Overview, key findings on adolescent drug use. 2020: 1-131. Ann Arbor: Institute for Social Research, University of Michigan.

3.2.1.3 Prevalence of Prescription Stimulant NMU in People with ADHD

Overall, 10.1% of respondents of the Applicant-submitted general population online survey, AR19.MA004, reported being diagnosed with ADHD, with 66.5% of those ever taking a prescription medication for ADHD (**Table 12**). Psychiatric comorbidities, including ADHD, were more common among people who reported lifetime prescription stimulant NMU than among individuals with NMU of prescription drugs other than stimulants or among people with no NMU of any prescription drug (**Figure 20**). For example, 8.7% of respondents with ADHD reported NMU of prescription stimulants in the past 30 days, whereas 1.0% of respondents without ADHD reported NMU of prescription stimulants in the past 30 days (**Figure 21**). As a comparison, 8.8% of respondents with ADHD reported NMU of prescription opioid analgesics in the past 30 days, whereas 3.0% of respondents without ADHD reported NMU of prescription opioid analgesics in the past 30 days.

Table 12. Lifetime diagnosis by a healthcare professional and prescription medication use for each diagnosis among people aged 18 to 49 years, AR19.MA004, an online survey of the general U.S. population conducted by the internet panel company YouGov

Lifetime Diagnosis	Lifetime Diagnosis (N=12,000)		Diagnosis Within Last 30 Days		Diagnosis Within Last Year		Diagnosis Longer Than 1 Year Ago		Ever Taken Prescription Medication for Diagnosis	
	n	% [*]	n	% [*]	n	% [*]	n	% [*]	n	% ^{**}
ADHD	1,207	10.1	135	1.1	251	2.1	956	8.0	803	66.5
Depression	4,189	34.9	476	4.0	1,108	9.2	3,081	25.7	3,089	73.7
Anxiety	4,173	34.8	565	4.7	1,255	10.5	2,918	24.3	2,619	62.8
Bipolar	997	8.3	171	1.4	340	2.8	657	5.5	545	54.7
Alcohol Substance Use Disorder	641	5.3	92	0.8	241	2.0	400	3.3	78	12.2
Drug Substance Use Disorder (other than Alcohol)	578	4.8	102	0.9	228	1.9	350	2.9	101	17.5
Conduct disorder	281	2.3	84	0.7	157	1.3	124	1.0	30	10.7
Oppositional defiant disorder	277	2.3	75	0.6	159	1.3	118	1.0	21	7.6
Learning disability	868	7.2	112	0.9	196	1.6	672	5.6	127	14.6
Other	1011	8.4	114	1.0	253	2.1	758	6.3	507	66.9[‡]

ADHD, Attention Deficit Hyperactivity Disorder; U.S., United States.

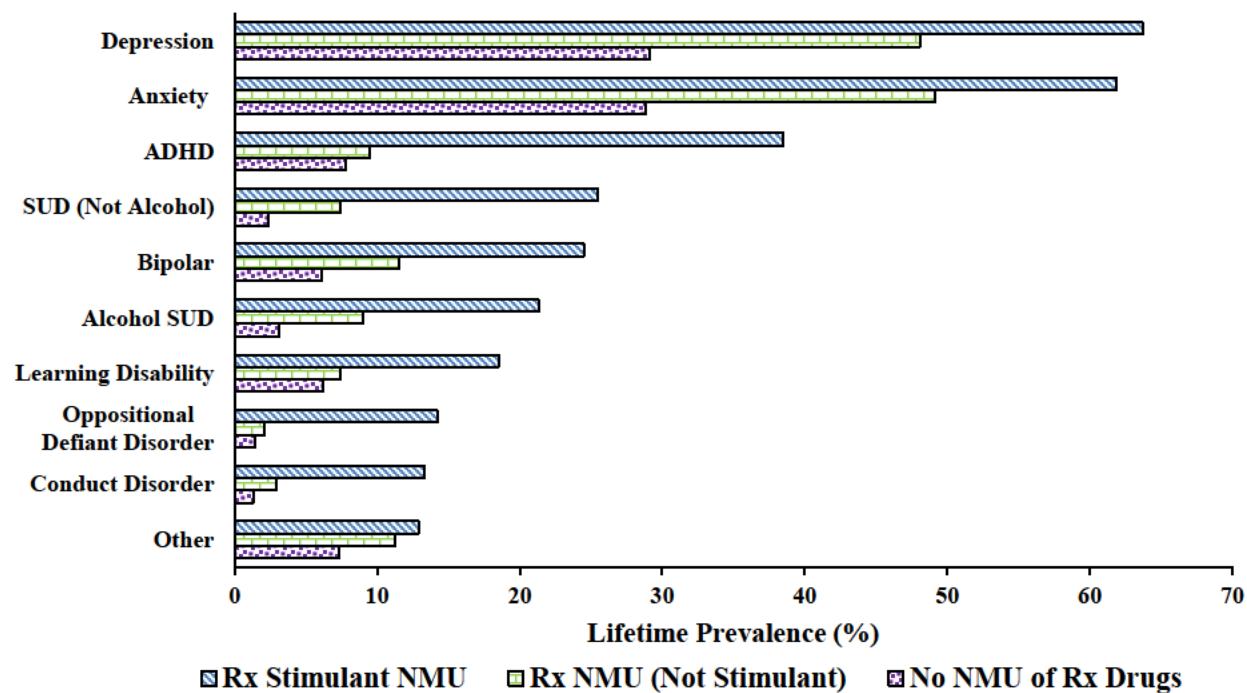
Note: ‘*’ refers to the percent of the total survey population (N=12,000).

Note: ‘**’ refers to the percent of respondents who reported lifetime diagnosis for respective condition.

Note: ‘‡’ this proportion is out of 758 due to missing data.

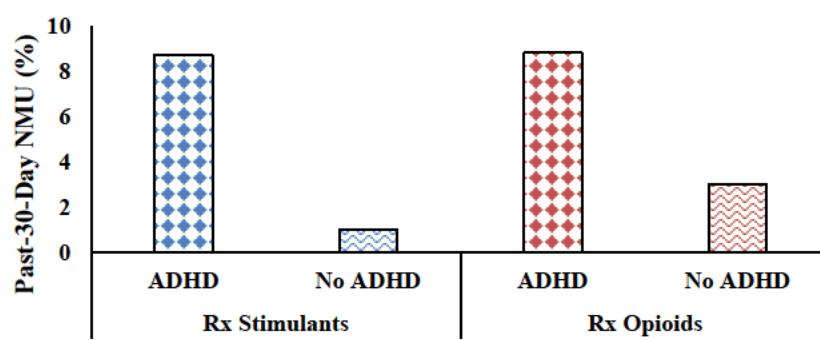
Source: Nonmedical Use of Prescription Medications among the General Population (AR19.MA004). Results from Table 2. Lifetime diagnosis by a healthcare professional and lifetime use of prescription medication to treat reported diagnosis.

Figure 20. Lifetime diagnoses by a healthcare professional among people aged 18 to 49 years, by NMU category, AR19.MA004, an online survey of the general U.S. population conducted by the internet panel company YouGov



ADHD, Attention Deficit Hyperactivity Disorder; NMU, nonmedical use; Rx, prescription; SUD, Substance Use Disorder; U.S., United States. Note: NMU is defined as use for any reason, even once, without your own prescription; Use in ways other than prescribed (such as taking more than prescribed, more often than prescribed, or for any other reason/way than prescribed; Use for the feeling or experience the medication caused (such as feeling of being high, enhancement of other drugs, prevention or treatment of withdrawal symptoms or other feelings). Source: FDA-generated figure. Nonmedical Use of Prescription Medications among the General Population (AR19.MA004). Results from Table 9. Lifetime diagnosis by a healthcare professional by NMU category.

Figure 21. NMU of prescription stimulants and opioid analgesics, among people aged 18 to 49 years, by ADHD diagnosis, AR19.MA004, an online survey of the general U.S. population conducted by the internet panel company YouGov



ADHD, Attention Deficit Hyperactivity Disorder; NMU, nonmedical use; Rx, prescription; U.S., United States. Note: NMU is defined as use for any reason, even once, without your own prescription; Use in ways other than prescribed (such as taking more than prescribed, more often than prescribed, or for any other reason/way than prescribed; Use for the feeling or experience the medication caused (such as feeling of being high, enhancement of other drugs, prevention or treatment of withdrawal symptoms or other feelings). Source: FDA-generated figure. Nonmedical Use of Prescription Medications among the General Population (AR19.MA004). Results from Table 69. NMU of prescription stimulants by ADHD diagnosis.

3.2.1.4 Scale of Prescription Stimulant NMU in People Seeking Advice or Healthcare

Calls to U.S. PCCs and U.S. ED visits can provide valuable information on the patterns and trends of prescription and illicit stimulant NMU. NPDS captures and compiles data from over two million human exposure cases from calls to PCCs across the entire United States involving exposures to prescription drugs, over-the-counter medications, foods, and unapproved products on a near real-time basis, offering insight into the reasons for and types of substances used by individuals as well as potential harms resulting from that use. The NEISS-CADES project provides a nationally representative sample of ED visits with medication-related AEs, providing insight into the reasons for and harms associated with the use of medications.

National Poison Data System Exposure Cases Involving Stimulants, by Reason

From 2001 through 2018, there were over 500,000 single-substance and multi-substance exposure cases uploaded to NPDS involving prescription²⁸ and illicit²⁹ stimulants, with around one-half of cases involving intentional exposures to prescription or illicit stimulants (**Table 13**). Over 63% of stimulant-involved NPDS exposure cases documented exposures to CII prescription stimulants (excluding regulated pharmaceutical cocaine), while around 20% documented exposures to cocaine, around 11% documented exposures to illicit methamphetamine, and over 6% documented exposures to unspecified amphetamines that could be prescription or illicit (amphetamine (NOS)).

²⁸ For analyses of NPDS data, CII prescription stimulants include the following APIs: amphetamine, dextroamphetamine, mixed amphetamine salts, lisdexamfetamine, methylphenidate, dexmethylphenidate, and methamphetamine. Regulated pharmaceutical cocaine and stimulants indicated for weight-loss (e.g., phentermine) are not included in the prescription stimulant category.

²⁹ For analyses of NPDS data, illicit stimulants include the following: regulated pharmaceutical and illicit cocaine (considered together) and illicit methamphetamine.

Table 13. National Poison Data System exposure cases involving prescription and illicit stimulants, by reason, 2001 to 2018

Reason	All Stimulant Exposure Cases		CII Prescription Stimulants [‡] (excluding regulated pharmaceutical cocaine)		Cocaine		Methamphetamine (Illicit)		Amphetamine (NOS)	
	N	%	N	%	N	%	N	%	N	%
Total	528,217	100.0%	333,915	100.0%	107,364	100.0%	60,260	100.0%	34,652	100.0%
Intentional*	260,334	49.3%	100,046	30.0%	95,381	88.8%	49,257	81.7%	22,637	65.3%
Unintentional**	233,638	44.2%	216,158	64.7%	5,660	5.3%	3,900	6.5%	8,387	24.2%
Adverse Reaction***	12,911	2.4%	10,831	3.2%	581	0.5%	602	1.0%	957	2.8%
Other/Unknown****	21,334	4.0%	6,880	2.1%	5,742	5.3%	6,501	10.8%	2,671	7.7%

CII, Schedule II; NOS, not otherwise specified.

Note: [‡] indicates CII stimulants only. Prescription stimulants include amphetamine, dextroamphetamine, amphetamine mixed salts, lisdexamfetamine, methylphenidate, dexmethylphenidate, and methamphetamine. Regulated pharmaceutical cocaine and stimulants indicated for weight-loss (e.g., phentermine) are not included.

Note: Reports of regulated pharmaceutical and illicit cocaine exposures are considered together.

Note: Amphetamine exposures not referencing a specific prescription or illicit product are considered "Amphetamine (NOS)."

Note: '*' includes "Intentional – Misuse; Abuse; Suspected Suicide; and Unknown" reasons.

Note: '**' includes "Unintentional – General and Therapeutic Error" reasons.

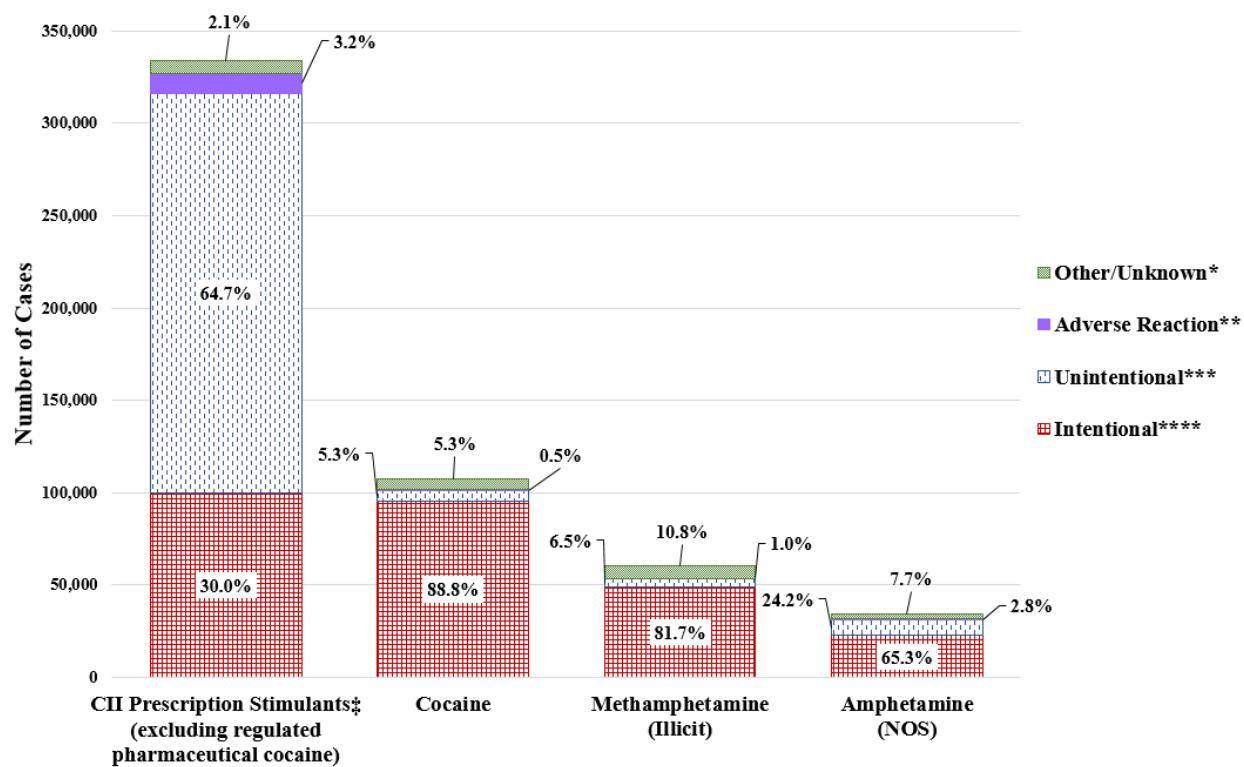
Note: '***' includes "Adverse Reaction – Drug; Food; and Other" reasons.

Note: '****' includes "Other - Contamination/Tampering; Malicious; and Withdrawal," "Unintentional - Bite/Sting; Environmental; Food Poisoning; Misuse; Occupational; and Unknown," and "Unknown Reason" categories.

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

From 2001 through 2018, almost two-thirds of NPDS exposure cases involving CII prescription stimulants were due to unintentional exposures, contrasting with cocaine, illicit methamphetamine, and amphetamine NOS exposure cases, where between 65% and 89% of cases were for intentional exposures (**Figure 22**). When these CII prescription stimulant exposure cases were examined by documented API, except for prescription methamphetamine, 57% to 79% of NPDS exposure cases involving individual prescription stimulant APIs were for unintentional exposure reasons, while over half of NPDS cases involving prescription methamphetamine documented intentional exposures (**Figure 23**), and followed a closer exposure reason pattern to illicit methamphetamine than to the other prescription stimulants. Methylphenidate products, followed by mixed amphetamine salt products were the most common prescription stimulant APIs involved in CII prescription stimulant NPDS exposure cases (42% and 37% of CII prescription stimulant exposure cases, respectively), while racemic amphetamine salt products were involved in 0.2% of CII prescription stimulant NPDS exposure cases across the eighteen-year time period.

Figure 22. National Poison Data System exposure cases involving prescription and illicit stimulants, by reason, 2001 to 2018



CII, Schedule II; NOS, Not otherwise specified.

Note: '‡' indicates CII stimulants only. Prescription stimulants include amphetamine, dextroamphetamine, amphetamine mixed salts, lisdexamfetamine, methylphenidate, dexmethylphenidate, and methamphetamine. Regulated pharmaceutical cocaine and stimulants indicated for weight-loss (e.g., phentermine) are not included.

Note: Reports of regulated pharmaceutical and illicit cocaine exposures are considered together.

Note: Amphetamine exposures not referencing a specific prescription or illicit product are considered "Amphetamine (NOS)."

Note: '*' includes "Other - Contamination/Tampering; Malicious; and Withdrawal," "Unintentional - Bite/Sting; Environmental; Food Poisoning; Misuse; Occupational; and Unknown," and "Unknown Reason" categories.

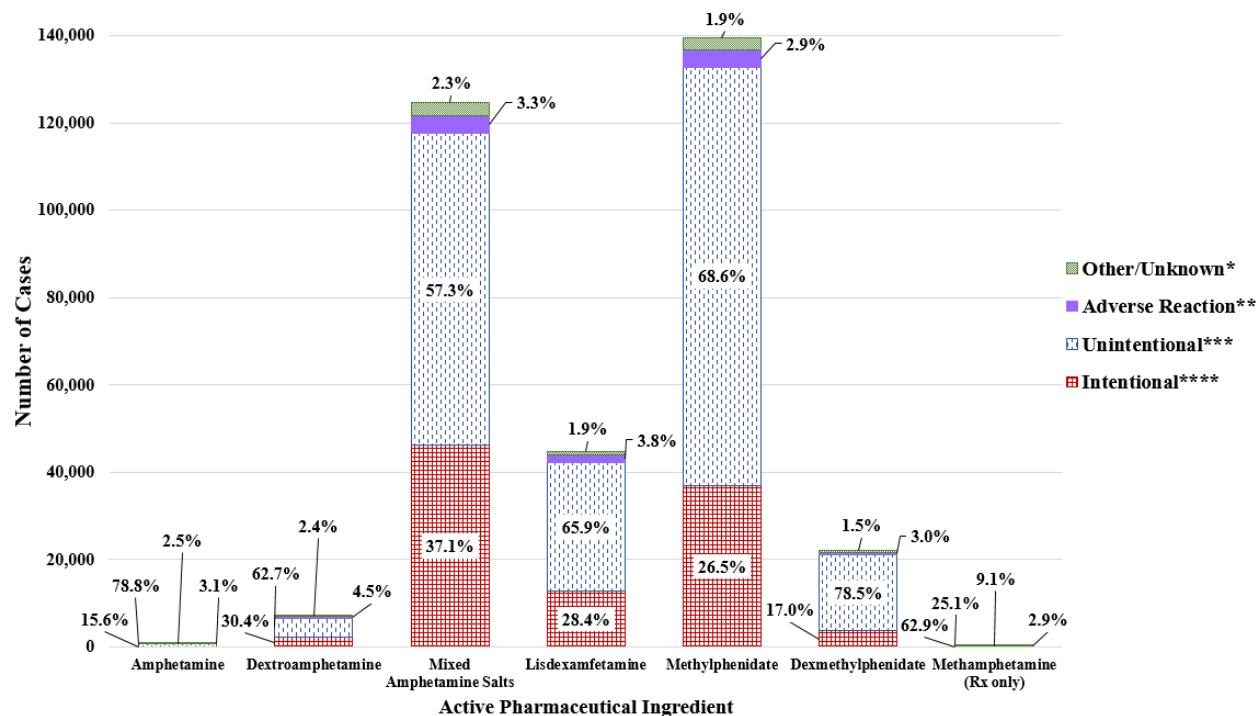
Note: '**' includes "Adverse Reaction - Drug; Food; and Other" reasons.

Note: '***' includes "Unintentional - General and Therapeutic Error" reasons.

Note: '****' includes "Intentional - Misuse; Abuse; Suspected Suicide; and Unknown" reasons.

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

Figure 23. National Poison Data System exposure cases involving prescription stimulant APIs, by reason, 2001 to 2018



API, active pharmaceutical ingredient; NOS, not otherwise specified; Rx, prescription.

Note: Schedule II stimulants only.

Note: Reports of regulated pharmaceutical and illicit cocaine exposures are considered together and are therefore excluded.

Note: Amphetamine exposures not referencing a specific prescription or illicit product are considered "Amphetamine (NOS)," and are also excluded.

Note: ** includes "Other - Contamination/Tampering; Malicious; and Withdrawal," "Unintentional - Bite/Sting; Environmental; Food Poisoning; Misuse; Occupational; and Unknown," and "Unknown Reason" categories.

Note: *** includes "Adverse Reaction - Drug; Food; and Other" reasons.

Note: **** includes "Unintentional - General and Therapeutic Error" reasons.

Note: ***** includes "Intentional - Misuse; Abuse; Suspected Suicide; and Unknown" reasons.

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

U.S. ED Visits Involving Prescription Stimulants, by Reason

From 2016 through 2018, there were estimated to be over 23,000 ED visits annually in the United States for AEs involving any CII prescription stimulant and over two million estimated ED visits annually for AEs involving medications other than CII prescription stimulants (**Table 14**). U.S. ED visits for harms from NMU of CII prescription stimulants accounted for over 40% of the estimated yearly ED visits for AEs involving any CII prescription stimulant, while ED visits for harms from therapeutic use of CII prescription stimulants accounted for around 30% of the estimated yearly ED visits for AEs involving any CII prescription stimulant. In comparison, ED visits for harms from NMU of other medications accounted for less than 16% of the estimated yearly ED visits for AEs involving any medication other than a CII prescription stimulant, while ED visits for harms from therapeutic use of other medications accounted for almost 69% of the estimated yearly ED visits for AEs involving any medication other than a CII prescription stimulant.

Table 14. National estimates of emergency department visits due to adverse events involving prescription stimulants and other medications, by reason of drug use, NEISS-CADES, 2016 to 2018

Reason of Drug Use	AEs Involving Prescription Stimulants (CII) ^a			AEs Involving Other Medications ^b		
	Cases	Average Annual National Estimate		Cases	Average Annual National Estimate	
		N	N		N	%
Total	1,194	23,576	100.0	95,932	2,058,753	100.0
Nonmedical Use	426	9,608	40.8	14,509	324,764	15.8
Self-Harm	278	5,199	22.1	13,395	269,874	13.1
Therapeutic Use	374	7,028	29.8	64,932	1,418,489	68.9
Unintended Pediatric Exposure	116	1,740	7.4	3,096	45,626	2.2

AE, adverse event; CII, Schedule II; ED, emergency department; NEISS-CADES, National Electronic Injury Surveillance System – Cooperative Adverse Drug Event Surveillance.

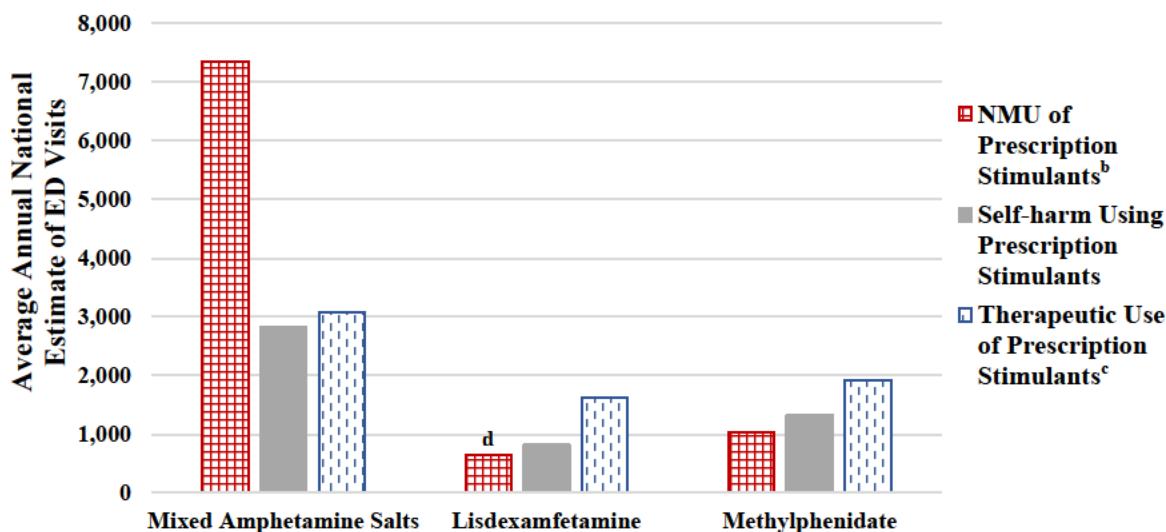
Note: ‘a’ includes ED visits for AEs in which at least one prescription amphetamine-related stimulant was implicated.

Note: ‘b’ includes ED visits for AEs in which in which other pharmaceutical products (i.e., not prescription amphetamine-related stimulants) were implicated.

Source: FDA-generated table. National Electronic Injury Surveillance System – Cooperative Adverse Drug Event Surveillance (NEISS-CADES) project, Centers for Disease Control and Prevention.

U.S. ED visits for AEs involving any CII prescription stimulant were also stratified by API. From 2016 through 2018, average annual estimates of ED visits for AEs involving CII prescription stimulants were highest for mixed amphetamine salt products compared to lisdexamfetamine and methylphenidate for all reasons of drug use. There were over 7,000 estimated ED visits per year for 2016 through 2018 for harms from NMU of mixed amphetamine salt products, while there were only around 3,000 estimated ED visits per year for harms from therapeutic use of mixed amphetamine salt products and around 3,000 estimated ED visits per year for harms from self-harm using mixed amphetamine salt products (**Figure 24**). National estimates for prescription racemic amphetamine sulfate, prescription dextroamphetamine, unspecified prescription amphetamine, and prescription dexmethylphenidate products are not reported as there were <20 surveillances cases or the total estimate of ED visits was <1200.

Figure 24. National estimates of emergency department visits due to adverse events involving prescription stimulant APIs, by reason of drug use: NEISS-CADES, 2016 to 2018^a



API, active pharmaceutical ingredient; CV, coefficient of variation; ED, emergency department; NMU, nonmedical use; NEISS-CADES, National Electronic Injury Surveillance System – Cooperative Adverse Drug Event Surveillance.

Note: National estimates for prescription racemic amphetamine sulfate, prescription dextroamphetamine, unspecified prescription amphetamine, and prescription dexmethylphenidate products are considered statistically unstable due to <20 cases or a total estimate <1200 for the three-year period 2016–2018 and are not shown.

Note: ‘a’ indicates that 116 cases (an estimated 1,740 annual visits) of unsupervised prescription stimulant exposures by children aged <5 years are not shown.

Note: ‘b’ includes abuse, therapeutic misuse, and overdoses without documentation of therapeutic intent, self-harm, abuse, or misuse.

Note: ‘c’ includes therapeutic adverse drug events (e.g., adverse effects, allergic reactions, supratherapeutic effects, and medication errors).

Note: ‘d’ estimate has a coefficient of variation >30% (CV = 35%) and may be statistically unstable.

Source: FDA-generated figure. National Electronic Injury Surveillance System – Cooperative Adverse Drug Event Surveillance (NEISS-CADES) project, Centers for Disease Control and Prevention.

Breakdown of Intentional Reasons for Stimulant Exposures in National Poison Data System Exposure Cases and U.S. ED Visits

Out of the 260,334 NPDS exposure cases involving prescription or illicit stimulants with an intentional exposure reason from 2001 through 2018, over 38% of cases involved prescription stimulants, over 36% of cases involved cocaine, almost 19% of cases involved illicit methamphetamine, and over 8% of cases involved unspecified amphetamines (Table 15).

Table 15. National Poison Data System exposure cases involving prescription and illicit stimulants, by intentional exposure reason, 2001 to 2018

Intentional Reason	All Stimulant Exposure Cases		CII Prescription Stimulants [‡] (excluding regulated pharmaceutical cocaine)		Cocaine		Methamphetamine (Illicit)		Amphetamine (NOS)	
	N	%	N	%	N	%	N	%	N	%
Total	260,334	100.0%	100,046	100.0%	95,381	100.0%	49,257	100.0%	22,637	100.0%
Nonmedical Use	131,735	50.6%	34,819	34.8%	54,154	56.8%	36,293	73.7%	10,498	46.4%
Abuse	100,877	38.7%	21,328	21.3%	44,641	46.8%	29,819	60.5%	8,700	38.4%
Misuse	30,858	11.9%	13,491	13.5%	9,513	10.0%	6,474	13.1%	1,798	7.9%
Suspected Suicide	113,406	43.6%	57,921	57.9%	36,753	38.5%	10,727	21.8%	10,553	46.6%
Unknown	15,193	5.8%	7,306	7.3%	4,474	4.7%	2,237	4.5%	1,586	7.0%

CII, Schedule II; NOS, not otherwise specified; NMU, nonmedical use.

Note: ‘‡’ indicates CII stimulants only. Prescription stimulants include amphetamine, dextroamphetamine, amphetamine mixed salts, lisdexamfetamine, methylphenidate, dexmethylphenidate, and methamphetamine. Regulated pharmaceutical cocaine and stimulants indicated for weight-loss (e.g., phentermine) are not included.

Note: Reports of regulated pharmaceutical and illicit cocaine exposures are considered together.

Note: Amphetamine exposures not referencing a specific prescription or illicit product are considered “Amphetamine (NOS).”

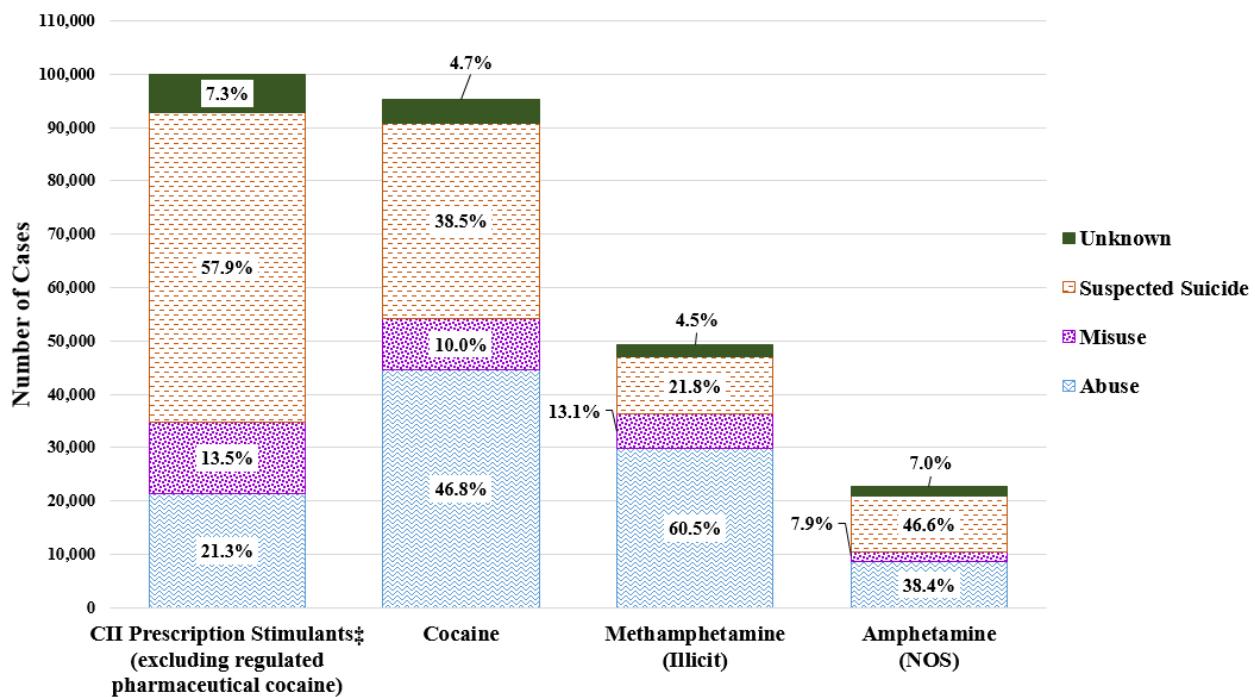
Note: NMU includes “Intentional – Misuse” or “Intentional – Abuse” reasons.

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

Over half of NPDS cases mentioning intentional exposures to CII prescription stimulants documented suspected suicide as the reason for exposure, while only around one-third of intentional CII prescription stimulant exposure cases documented NMU (i.e., cases categorized as “Intentional – Misuse” or “Intentional – Abuse”) as the exposure reason. Compared to CII prescription stimulants, intentional exposure case reasons were very different for cocaine and illicit methamphetamine exposures. The majority of NPDS intentional exposure cases for cocaine and illicit methamphetamine were for NMU reasons, and most of those cases were for intentional abuse (**Figure 25**).

For all CII prescription stimulant APIs except prescription methamphetamine, the most common intentional exposure reason for NPDS cases was suspected suicide (51% to 65%) (**Figure 26**). However, for intentional exposure cases involving prescription methamphetamine, over half of the cases documented NMU as the reason for the exposure, similar to illicit methamphetamine, as shown in **Figure 25**.

Figure 25. National Poison Data System exposure cases involving prescription and illicit stimulants, by intentional exposure reason, 2001 to 2018



CII, Schedule II; NOS, Not otherwise specified

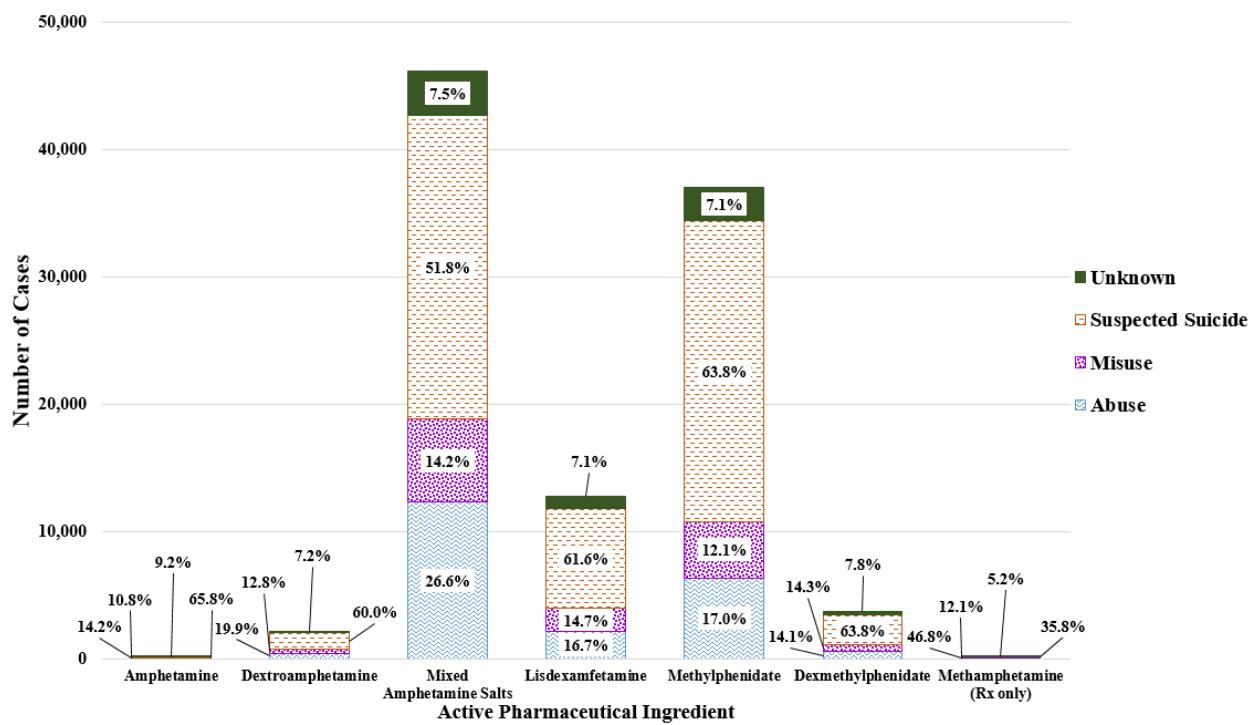
Note: '‡' indicates CII stimulants only. Prescription stimulants include amphetamine, dextroamphetamine, amphetamine mixed salts, lisdexamfetamine, methylphenidate, dextroamphetamine, and methamphetamine. Regulated pharmaceutical cocaine and stimulants indicated for weight-loss (e.g., phentermine) are not included.

Note: Reports of regulated pharmaceutical and illicit cocaine exposures are considered together.

Note: Amphetamine exposures not referencing a specific prescription or illicit product are considered "Amphetamine (NOS)." Note: NMU includes "Intentional – Misuse" or "Intentional – Abuse" reasons.

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

Figure 26. National Poison Data System exposure cases involving prescription stimulant APIs, by intentional exposure reason, 2001 to 2018



API, active pharmaceutical ingredient; NOS, not otherwise specified; Rx, prescription.

Note: Schedule II stimulants only.

Note: Reports of regulated pharmaceutical and illicit cocaine exposures are considered together and are therefore excluded.

Note: Amphetamine exposures not referencing a specific prescription or illicit product are considered "Amphetamine (NOS)," and are also excluded.

Note: NMU includes "Intentional – Misuse" or "Intentional – Abuse" reasons.

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

From 2016 through 2018, among ED visits for harms from NMU (i.e., abuse, therapeutic misuse, and overdoses without indication of intent) of prescription stimulants, an estimated 5,119 annual ED visits involved documented abuse of CII prescription stimulants (21.7% of estimated ED visits for AEs involving CII prescription stimulants) and an estimated 1,552 annual ED visits involved therapeutic misuse of CII prescription stimulants (6.6% of estimated ED visits for AEs involving CII prescription stimulants), while an estimated 130,487 annual ED visits involved documented abuse of medications other than CII prescription stimulants (6.3% of estimated ED visits for AEs involving medications other than stimulants) and an estimated 55,489 annual ED visits involved therapeutic misuse of medications other than CII prescription stimulants (2.7% of estimated ED visits for AEs involving medications other than stimulants) (Table 16).

Table 16. National estimates of emergency department visits due to adverse events involving prescription stimulants and other medications, by nonmedical reason of drug use: NEISS-CADES, 2016 to 2018

Nonmedical Reason of Drug Use	AEs Involving Prescription Stimulants (CII) ^a			AEs Involving Other Medications ^b		
	Cases	Average Annual National Estimate	Cases	Average Annual National Estimate		
	N	N	% of Total Visits	N	N	% of Total Visits
Total Nonmedical Use	426	9,608	40.8	14,509	324,764	15.8
Documented Abuse	224	5,119	21.7	6,098	130,487	6.3
Overdoses without Indication of Intent	124	2,937	12.5	5,849	138,787	6.7
Therapeutic Misuse	78	1,552	6.6	2,562	55,489	2.7

AE, adverse event; CII, Schedule II; ED, emergency department; NEISS-CADES, National Electronic Injury Surveillance System – Cooperative Adverse Drug Event Surveillance.

Note: ‘a’ includes ED visits for AEs in which at least one prescription amphetamine-related stimulant was implicated.

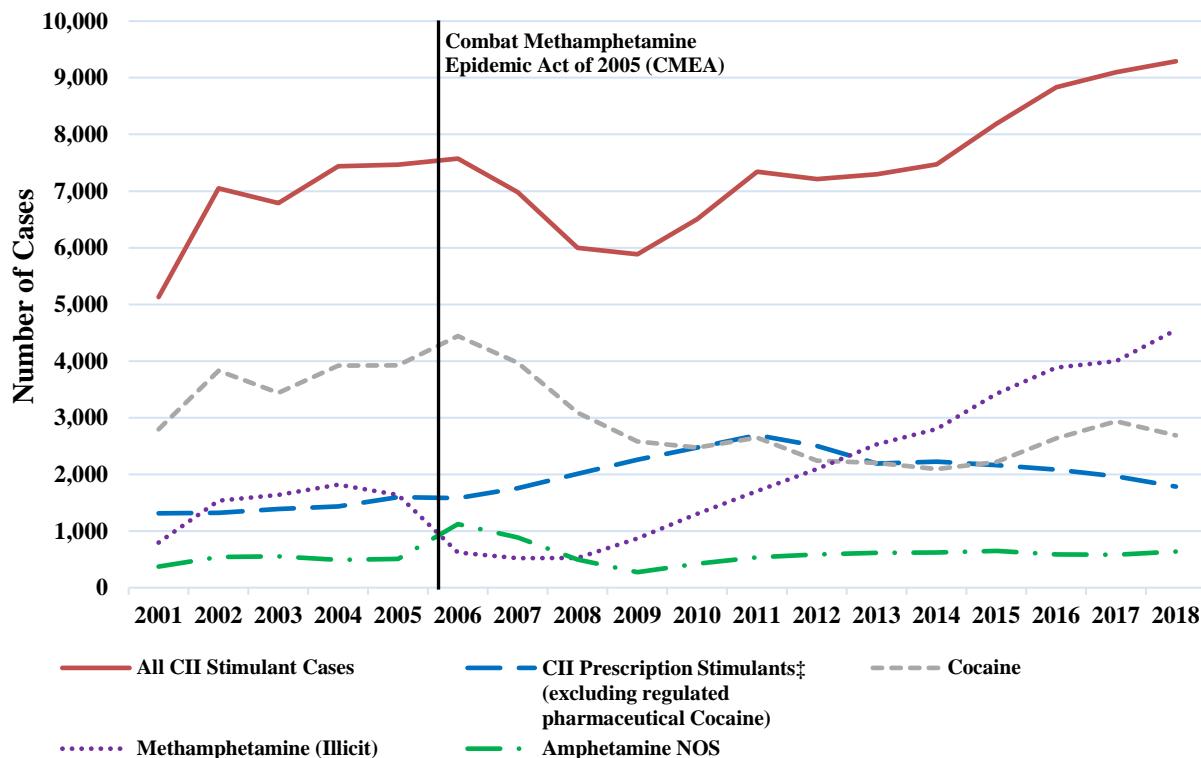
Note: ‘b’ includes ED visits for AEs in which in which other pharmaceutical products (i.e., not prescription amphetamine-related stimulants) were implicated.

Source: FDA-generated table. National Electronic Injury Surveillance System – Cooperative Adverse Drug Event Surveillance (NEISS-CADES) project, Centers for Disease Control and Prevention.

Trends in National Poison Data System Exposure Cases Involving NMU of Stimulants

Trends in NPDS exposure cases reporting NMU of prescription and illicit stimulants from 2001 through 2018 are presented in (Figure 27). Overall, NPDS exposure cases involving NMU of all stimulants increased from 2001 through 2018. When trends in NPDS exposure cases involving NMU were stratified by stimulant category, however, the increase in cases were largely driven by steady increases in NMU cases involving illicit methamphetamine, especially starting around 2008. This increase in cases involving NMU of illicit methamphetamine followed a short but sharp decrease in illicit methamphetamine cases around the time the Combat Methamphetamine Epidemic Act of 2005 was signed into law, in March 2006. CII prescription stimulant NMU cases peaked in 2011 and slowly decreased through the end of 2018, while NPDS cases involving NMU of cocaine and amphetamine NOS remained steady across the eighteen-year period.

Figure 27. National Poison Data System exposure cases involving NMU of prescription and illicit stimulants, 2001 to 2018



CII, Schedule II; NMU, nonmedical use; NOS, not otherwise specified.

Note: '‡' indicates CII stimulants only. Prescription stimulants include amphetamine, dextroamphetamine, amphetamine mixed salts, lisdexamfetamine, methylphenidate, dexmethylphenidate, and methamphetamine. Regulated pharmaceutical cocaine and stimulants indicated for weight-loss (e.g., phentermine) are not included.

Note: Reports of regulated pharmaceutical and illicit cocaine exposures are considered together.

Note: Amphetamine exposures not referencing a specific prescription or illicit product are considered "Amphetamine (NOS)." Note: NMU consists of "Intentional – Misuse" and "Intentional – Abuse" exposures.

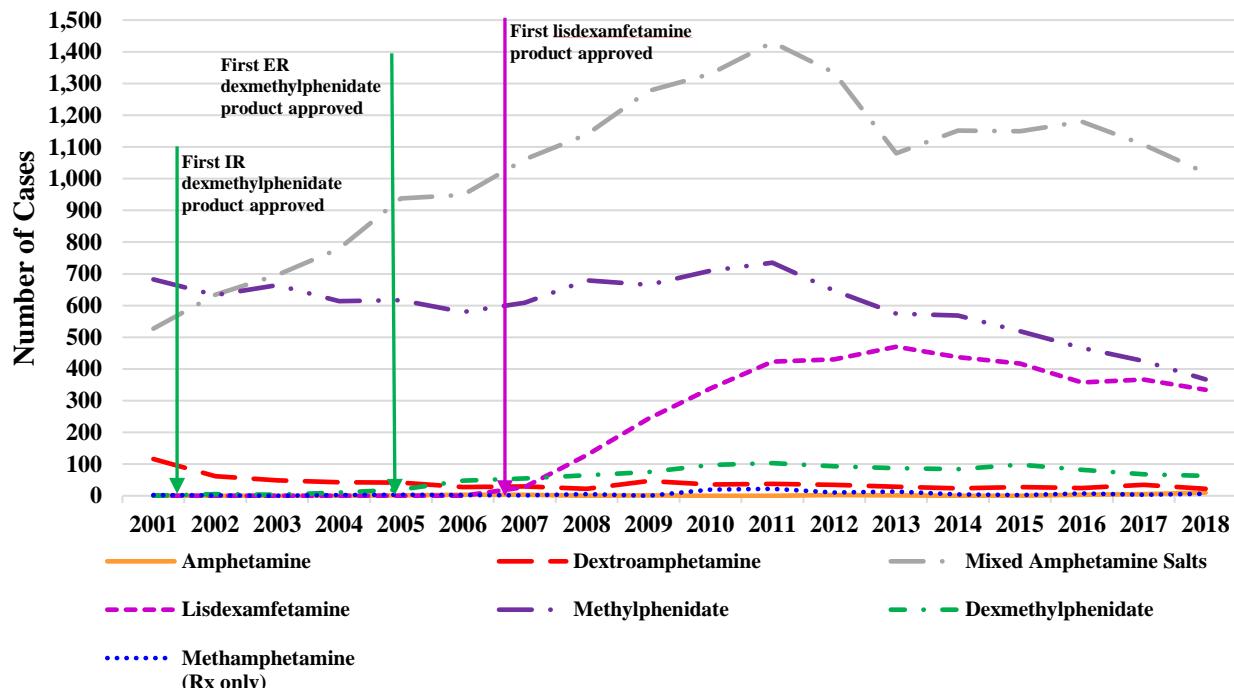
Note: Excludes prescription and illicit stimulant exposure cases with "Intentional - Suspected Suicide" or "Intentional - Unknown" reasons.

Note: Children 5 years and younger (N = 187) are not included.

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

We further stratified trends in NPDS exposure cases involving NMU of CII prescription stimulants by prescription stimulant API. Across the majority of the eighteen-year period, the most common prescription stimulant API involved in NMU NPDS exposure cases was mixed amphetamine salt products (**Figure 28**). Amphetamine, dextroamphetamine, and prescription methamphetamine NMU cases remained stable from 2001 through 2018. The first IR dexmethylphenidate product was approved in November 2001 and the first ER dexmethylphenidate product was approved in May 2005. Increases in NMU cases occurred after both approvals; this trend was also seen after the first lisdexamfetamine product was approved in February 2007. However, NMU cases for both APIs either stabilized or started to decrease in recent years, and this decrease was also seen with methylphenidate and mixed amphetamine salt stimulant products. Overall, NPDS exposure cases involving NMU of each CII prescription stimulant API have followed similar trends observed with drug utilization patterns of prescription stimulants by API between 2014 and 2019, as previously shown in **Figure 3**.

Figure 28. National Poison Data System exposure cases involving NMU of prescription stimulants, by API, 2001 to 2018



API, active pharmaceutical ingredient; IR, immediate-release; ER, extended-release; NMU, nonmedical use; NOS, not otherwise specified; Rx, prescription.

Note: Schedule II stimulants only.

Note: Reports of regulated pharmaceutical and illicit cocaine exposures are considered together and are therefore excluded.

Note: Amphetamine exposures not referencing a specific prescription or illicit product are considered "Amphetamine (NOS)," and are also excluded.

Note: NMU consists of "Intentional – Misuse" and "Intentional – Abuse" exposures.

Note: Excludes prescription stimulant exposure cases with "Intentional - Suspected Suicide" or "Intentional - Unknown" reasons.

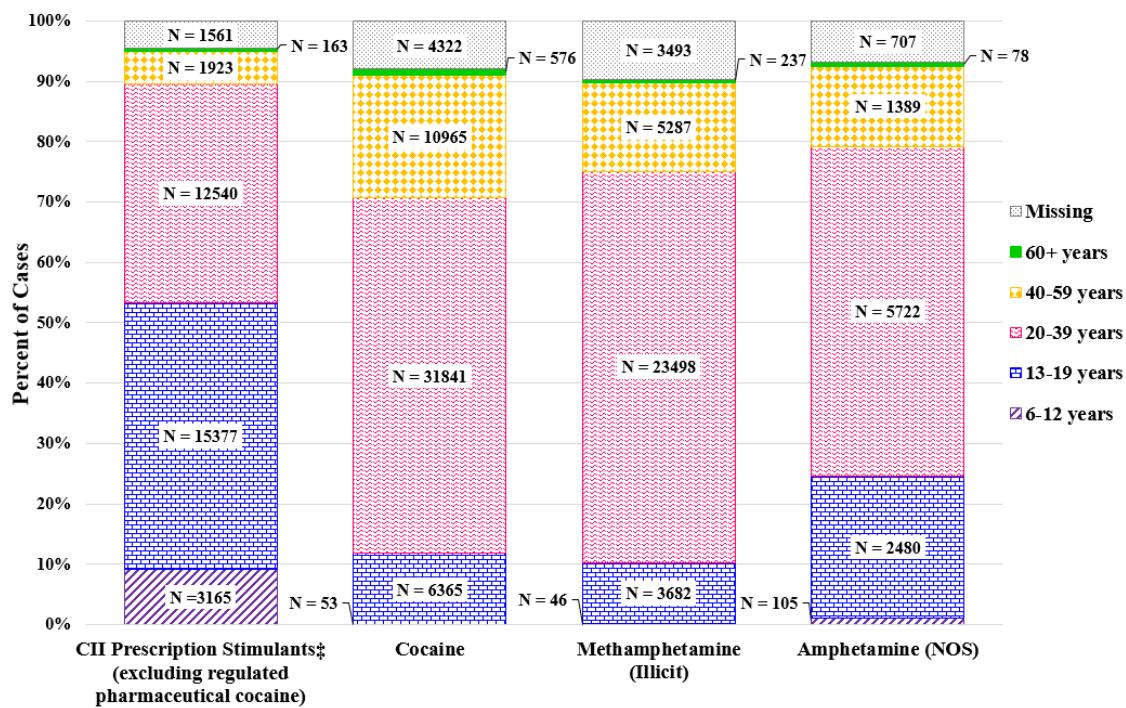
Note: Children 5 years and younger (N = 90) are not included.

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

National Poison Data System Exposure Cases and U.S. ED Visits Involving NMU of Stimulants, by Age

Figure 29 shows the total aggregated number and percent of NPDS exposure cases involving NMU of prescription and illicit stimulants from 2001 through 2018, by age. For all CII prescription stimulants, including prescription methamphetamine, over half of NMU NPDS cases were for people less than 20 years of age, and almost 90% of CII prescription stimulant NMU cases were for individuals less than 40 years of age. Almost 10% of CII prescription stimulant NMU cases, however, were for children between 6 and 12 years of age. In comparison, over half of NPDS exposure cases involving NMU of cocaine, illicit methamphetamine, and amphetamine NOS were for people between 20 and 39 years of age, while only between 10% and 30% of cases were for people less than 20 years of age.

Figure 29. National Poison Data System exposure cases involving NMU of prescription and illicit stimulants, by age, 2001 to 2018



CII, Schedule II; NMU, nonmedical use; NOS, not otherwise specified.

Note: ‘‡’ indicates CII stimulants only. Prescription stimulants include amphetamine, dextroamphetamine, amphetamine mixed salts, lisdexamfetamine, methylphenidate, dextroamphetamine, and methamphetamine. Regulated pharmaceutical cocaine and stimulants indicated for weight-loss (e.g., phentermine) are not included.

Note: Reports of regulated pharmaceutical and illicit cocaine exposures are considered together.

Note: Amphetamine exposures not referencing a specific prescription or illicit product are considered “Amphetamine (NOS).”

Note: NMU consists of “Intentional – Misuse” and “Intentional – Abuse” exposures.

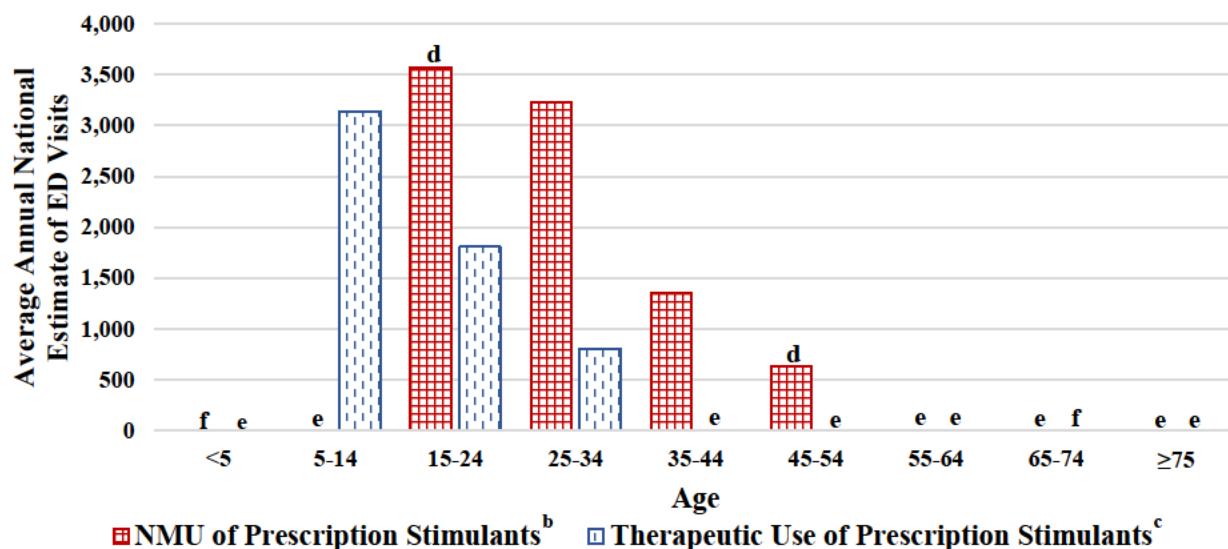
Note: Excludes prescription and illicit stimulant exposure cases with “Intentional - Suspected Suicide” or “Intentional - Unknown” reasons.

Note: Children 5 years and younger (N = 187) are not included.

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

From 2016 through 2018, among U.S. ED visits for harms from NMU of CII prescription stimulants, the highest annual national estimate (3,577 ED visits/year) involved people between the ages of 15 and 24 years (coefficient of variation (CV)=32%) and people between the ages of 25 and 34 years (3,232 ED visits/year) (**Figure 30**). ED visits for harms from therapeutic use of CII prescription stimulants involved younger people than ED visits for harms from NMU of CII prescription stimulants, as the highest annual national estimate of ED visits (3,143 ED visits/year) involved people between the ages of 5 and 14 years. National estimates of ED visits for harms from NMU of CII prescription stimulants are not reported for the following age groups: <5 years, 5-14 years, 55-64 years, 65-74 years, and ≥75 years because of too few surveillance cases in the sample (<20 cases) or total estimates <1200 ED visits. National estimates of ED visits for harms from therapeutic use of CII prescription stimulants are not reported for the following age groups: <5 years, 35-44 years, 45-54 years, 55-64 years, 65-74 years, and ≥75 years for the same reason.

Figure 30. National estimates of emergency department visits due to adverse events involving prescription stimulants, reason of drug use by age: NEISS-CADES, 2016 to 2018^a



CV, coefficient of variation; ED, emergency department; NEISS-CADES, National Electronic Injury Surveillance System – Cooperative Adverse Drug Event Surveillance; NMU, nonmedical use.

Note: 'a' indicates that 116 cases (an estimated 1,740 annual visits) of unsupervised prescription stimulant exposures by children aged <5 years are not included.

Note: 'b' includes abuse, therapeutic misuse, and overdoses without documentation of therapeutic intent, self-harm, abuse, or misuse.

Note: 'c' includes therapeutic adverse drug events (e.g., adverse effects, allergic reactions, supratherapeutic effects, and medication errors).

Note: 'd' indicates estimate has a coefficient of variation >30% (CV = 32% and 31%, respectively) and may be statistically unstable.

Note: 'e' indicates estimates based on <20 cases or total estimates <1,200 for the three-year period 2016-2018 are considered statistically unstable and are not shown.

Note: 'f' indicates zero documented cases in the age category.

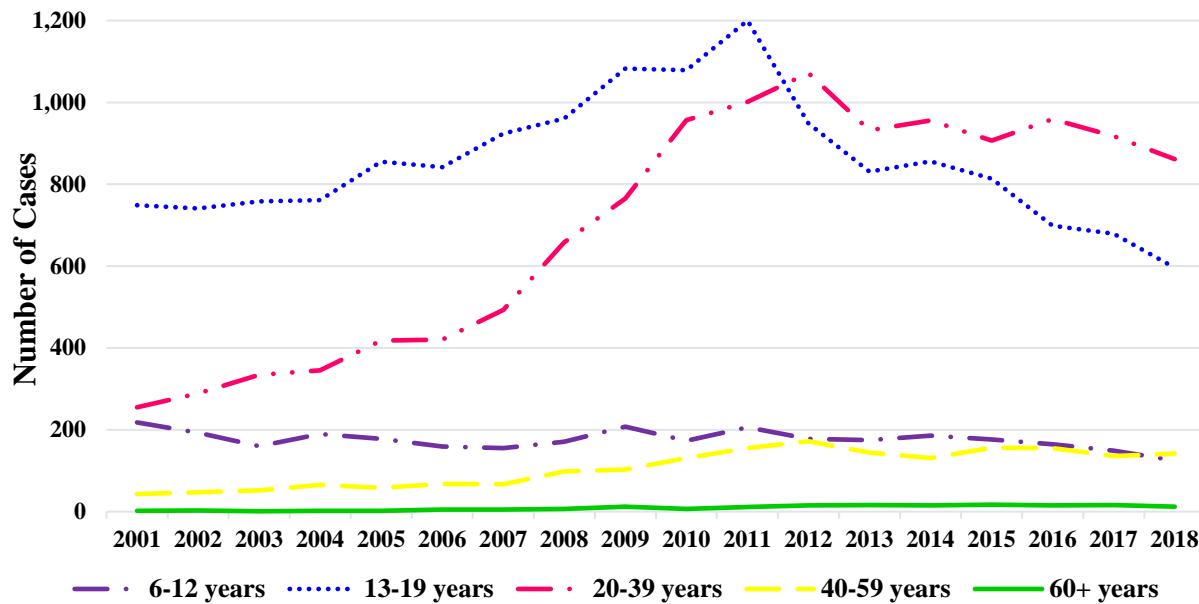
Note: Excludes emergency department visits due to self-harm using prescription stimulants.

Source: FDA-generated figure. National Electronic Injury Surveillance System – Cooperative Adverse Drug Event Surveillance (NEISS-CADES) project, Centers for Disease Control and Prevention.

Trends in National Poison Data System Exposure Cases Involving NMU of Stimulants, by Age

We also analyzed trends in NPDS exposure cases involving NMU of prescription and illicit stimulants in people six years and older from 2001 through 2018. **Figure 31** illustrates the change in prescription stimulant NMU NPDS exposure cases, stratified by age, over the eighteen-year time period. People between ages 13 to 19 years and 20 to 39 years had the largest number of NPDS NMU cases involving CII prescription stimulants across the entire eighteen-year time period. The number of NMU cases for these age groups peaked between 2011 and 2012 and have slightly decreased through 2018, contributing to the overall decreasing trend in NMU cases across all ages for CII prescription stimulants shown in **Figure 27, above**. As a comparison, NPDS exposure cases involving NMU of CII prescription stimulants remained stable over the eighteen-year period for children less than 12 years and for adults greater than 40 years.

Figure 31. National Poison Data System exposure cases involving NMU of CII prescription stimulants[‡] (excluding regulated pharmaceutical cocaine), by year and age, 2001 to 2018



CII, Schedule II; NMU, nonmedical use.

Note: ‘‡’ indicates CII stimulants only. Prescription stimulants include amphetamine, dextroamphetamine, amphetamine mixed salts, lisdexamfetamine, methylphenidate, dexmethylphenidate, and methamphetamine. Regulated pharmaceutical cocaine and stimulants indicated for weight-loss (e.g., phentermine) are not included.

Note: NMU consists of “Intentional – Misuse” and “Intentional – Abuse” exposures.

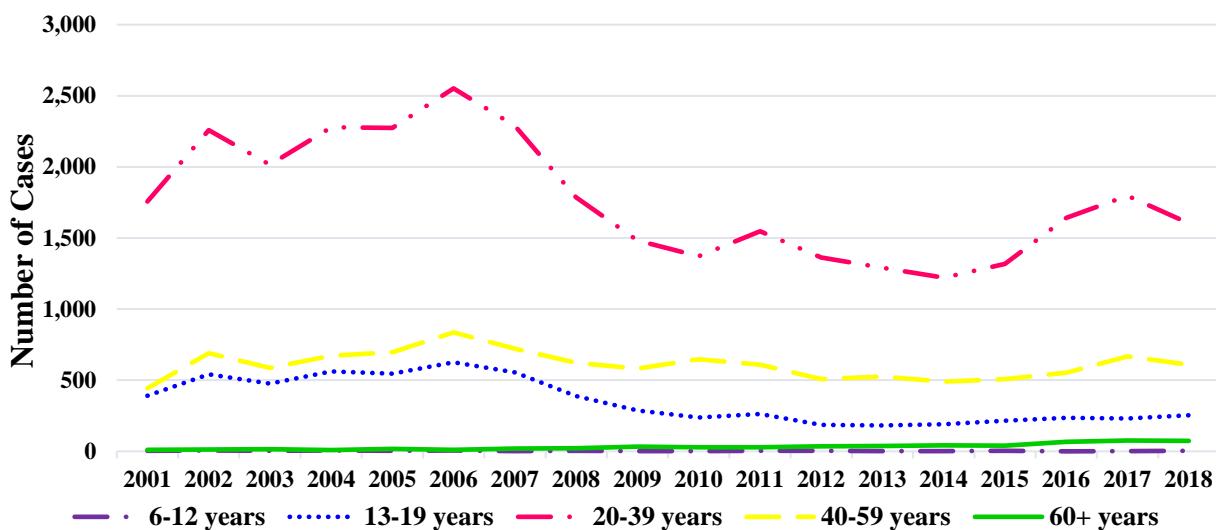
Note: Excludes prescription stimulant exposure cases with “Intentional - Suspected Suicide” or “Intentional - Unknown” reasons.

Note: Children 5 years and younger (N = 90) and exposure cases with missing age (N = 1561) are not included.

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

NPDS exposure cases involving NMU of cocaine from 2001 through 2018 followed a different trend than CII prescription stimulants, as the largest number of NMU exposure cases involving cocaine across the entire eighteen-year time period was seen in people aged 20 to 39 years followed by people aged 40 to 59 years and peaked in 2006 (Figure 32). However, trends for NPDS NMU cases involving illicit methamphetamine were very different from both CII prescription stimulants and cocaine across the same eighteen-year time period. Figure 33 shows that unlike CII prescription stimulants and cocaine, there has been a significant increase in illicit methamphetamine NMU NPDS exposure cases since 2008, especially in people aged 20 to 39 years. This increase followed a short but sharp decrease in exposure cases around the time the Combat Methamphetamine Epidemic Act of 2005 was signed into law.

Figure 32. National Poison Data System exposure cases involving NMU of cocaine, by year and age, 2001 to 2018



NMU, nonmedical use.

Note: Reports of regulated pharmaceutical and illicit cocaine exposures are considered together.

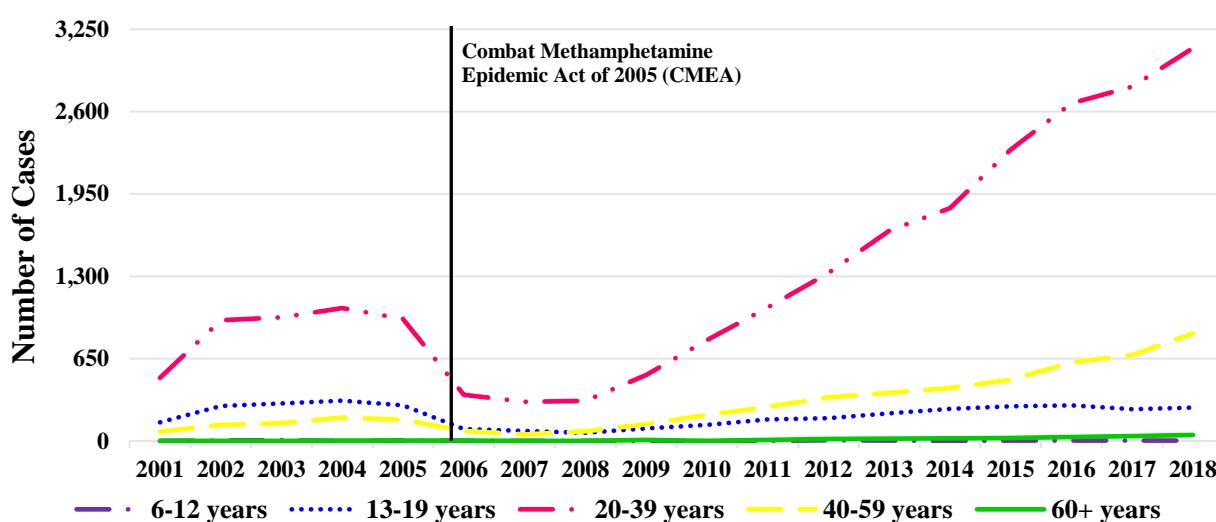
Note: NMU consists of "Intentional – Misuse" and "Intentional – Abuse" exposures.

Note: Excludes regulated pharmaceutical and illicit cocaine exposure cases with "Intentional - Suspected Suicide" or "Intentional - Unknown" reasons.

Note: Children 5 years and younger (N = 32) and exposure cases with missing age (N = 4322) are not included.

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

Figure 33. National Poison Data System exposure cases involving NMU of illicit methamphetamine, by year and age, 2001 to 2018



NMU, nonmedical use.

Note: Illicit methamphetamine only.

Note: NMU consists of "Intentional – Misuse" and "Intentional – Abuse" exposures.

Note: Excludes illicit methamphetamine exposure cases with "Intentional - Suspected Suicide" or "Intentional - Unknown" reasons.

Note: Children 5 years and younger (N = 50) and exposure cases with missing age (N = 3493) are not included.

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

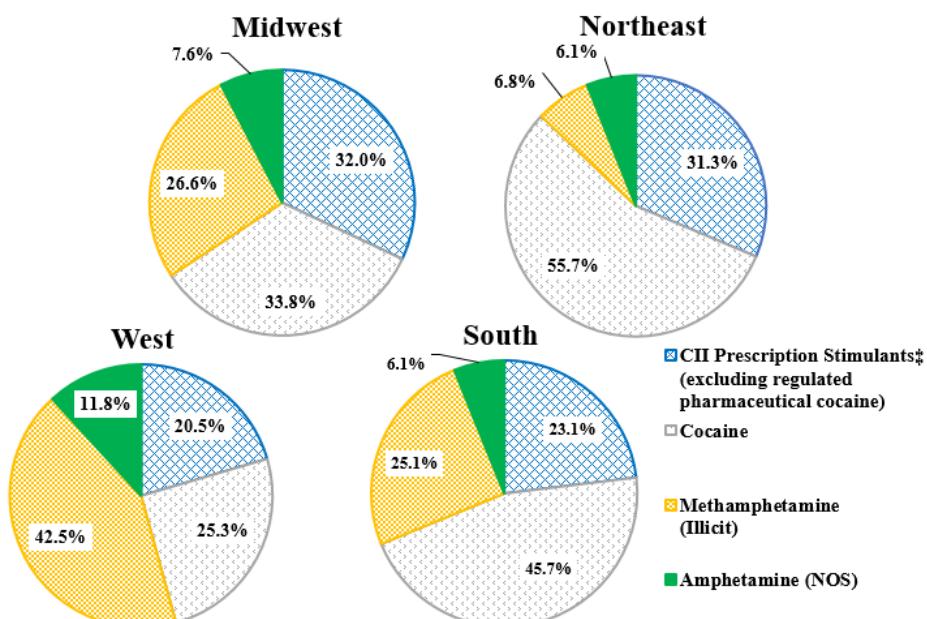
Source: U.S. Department of Justice, Drug Enforcement Administration: Diversion Control Division [Internet]. General Information Regarding the Combat Methamphetamine Epidemic Act of 2005 [Title VII of Public Law 109-177]. Available at:

<https://www.deadiversion.usdoj.gov/meth/cma2005.htm>. (accessed April 14, 2020).

Regional Differences in Type of Stimulant Involved in National Poison Data System NMU Exposure Cases for Stimulants

From 2001 through 2018, aggregated NPDS exposure cases involving NMU prescription and illicit stimulants demonstrated regional differences in NMU by stimulant category. The majority of NPDS exposure cases involving prescription and illicit stimulants in the Northeast region of the United States involved cocaine or CII prescription stimulants, with less than 7% of cases having documented exposures to illicit methamphetamine. This was very different from NMU cases in the West, where almost half of cases involved illicit methamphetamine exposures (**Figure 34**).

Figure 34. National Poison Data System exposure cases involving NMU of prescription and illicit stimulants, by region, 2001 to 2018



CII, Schedule II; NMU, nonmedical use; NOS, not otherwise specified.

Note: * indicates CII stimulants only. Prescription stimulants include amphetamine, dextroamphetamine, amphetamine mixed salts, lisdexamfetamine, methylphenidate, dexmethylphenidate, and methamphetamine. Regulated pharmaceutical cocaine and stimulants indicated for weight-loss (e.g., phentermine) are not included.

Note: Reports of regulated pharmaceutical and illicit cocaine exposures are considered together.

Note: Amphetamine exposures not referencing a specific prescription or illicit product are considered "Amphetamine (NOS)."

Note: NMU consists of "Intentional – Misuse" and "Intentional – Abuse" exposures.

Note: Excludes prescription and illicit stimulant exposure cases with "Intentional - Suspected Suicide" or "Intentional - Unknown" reasons.

Note: Children 5 years and younger (N = 187) are not included.

Note: Percentages are calculated using total drug mentions for each region.

Note: Further information on the composition of each region is described in **Table 72 of Section 3.6**.

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

3.2.1.5 Prescription Stimulant NMU in Enriched Populations: People Being Assessed for or Entering Treatment for SUD

Adults and adolescents being assessed for substance abuse problems and treatment planning can serve as an integral source of information for the evaluation of NMU of prescription stimulants. The TEDS database compiles information gathered from the approximately two million people being admitted to publicly funded treatment programs each year, offering some insights into the drugs people most often report as their primary, secondary, and tertiary drugs of abuse. **Table 17** shows that, in 2017, the most common substance people reported as their primary drug was opiates (34.0%), with over three quarters of that being heroin, followed by alcohol (29.5%). Stimulants accounted for 12.0% of primary substances

reported in 2017, with nearly 95% of these being methamphetamine. Therefore, amphetamines and other stimulants collectively accounted for less than 1% of primary substances reported.

Table 17. Admissions for people age 12 years or older, by primary substance use at admission, percent distribution, Treatment Episode Data Set, 2007 to 2017³⁰

Primary substance	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017
Total	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0
Alcohol	39.0	39.6	40.1	39.0	37.8	37.2	35.5	34.3	32.1	31.4	29.5
Alcohol only	21.6	22.2	22.4	21.4	20.7	20.5	20.0	19.1	18.0	17.8	16.6
Alcohol w/ secondary drug	17.4	17.5	17.7	17.5	17.0	16.7	15.5	15.3	14.1	13.7	12.8
Opiates	18.5	19.8	21.4	23.0	25.1	26.6	28.7	30.7	33.8	33.7	34.0
Heroin	13.5	13.8	14.3	14.2	15.0	16.8	19.7	22.6	25.8	25.9	26.6
Other opiates/synthetics	5.0	6.0	7.1	8.8	10.1	9.7	9.1	8.1	8.0	7.7	7.4
Non-Rx methadone	0.3	0.3	0.3	0.3	0.4	0.3	0.3	0.3	0.2	0.2	0.2
Other opiates/synthetics	4.7	5.7	6.8	8.4	9.7	9.4	8.8	7.8	7.8	7.6	7.2
Cocaine	12.9	11.4	9.3	8.1	7.7	6.8	6.0	5.3	4.9	4.8	5.1
Smoked cocaine	9.3	8.2	6.8	5.8	5.4	4.7	4.1	3.5	3.2	3.0	3.0
Non-smoked cocaine	3.6	3.2	2.6	2.3	2.4	2.1	1.9	1.8	1.7	1.9	2.1
Marijuana/hashish	16.0	17.3	18.2	18.6	18.4	17.5	16.7	15.4	14.3	13.6	12.5
Stimulants	10.1	8.4	7.6	7.9	7.6	8.5	9.8	10.7	10.4	12.1	12.0
Methamphetamine	9.7	7.9	7.2	7.3	7.1	8.0	9.2	10.2	9.9	11.5	11.4
Other amphetamines	0.3	0.3	0.4	0.5	0.4	0.5	0.5	0.5	0.5	0.4	0.4
Other stimulants	0.1	0.1	0.1	0.1	0.1	*	*	*	0.1	0.1	0.1
Other drugs	1.5	1.7	1.9	2.2	2.2	2.1	2.1	2.0	2.2	2.4	2.3
Tranquilizers	0.6	0.6	0.7	0.8	0.9	0.9	0.9	0.9	0.9	1.0	1.0
Benzodiazepines	0.5	0.6	0.7	0.8	0.9	0.9	0.9	0.9	0.9	1.0	1.0
Other tranquilizers	*	*	*	*	*	*	*	*	*	*	*
Sedatives/hypnotics	0.2	0.2	0.3	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2
Barbiturates	0.1	0.1	0.1	0.1	*	*	0.1	0.1	0.1	0.1	0.1
Other sedatives/hypnotics	0.2	0.2	0.2	0.2	0.2	0.1	0.1	0.1	0.1	0.1	0.1
Hallucinogens	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
PCP	0.2	0.2	0.2	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3
Inhalants	0.1	0.1	0.1	0.1	0.1	0.1	0.1	*	*	0.1	*
Over-the-counter	*	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	*
Other	0.3	0.4	0.5	0.6	0.5	0.5	0.5	0.5	0.6	0.7	0.7
None reported	2.0	1.7	1.4	1.3	1.2	1.3	1.2	1.6	2.3	2.0	4.6

PCP, phencyclidine; Rx, prescription.

Note: Based on administrative data reported to TEDS by all reporting states and jurisdictions. Admissions for which values were not collected, unknown, or missing are excluded from the percentage base (denominator).

Note: '*' indicates less than 0.05 percent.

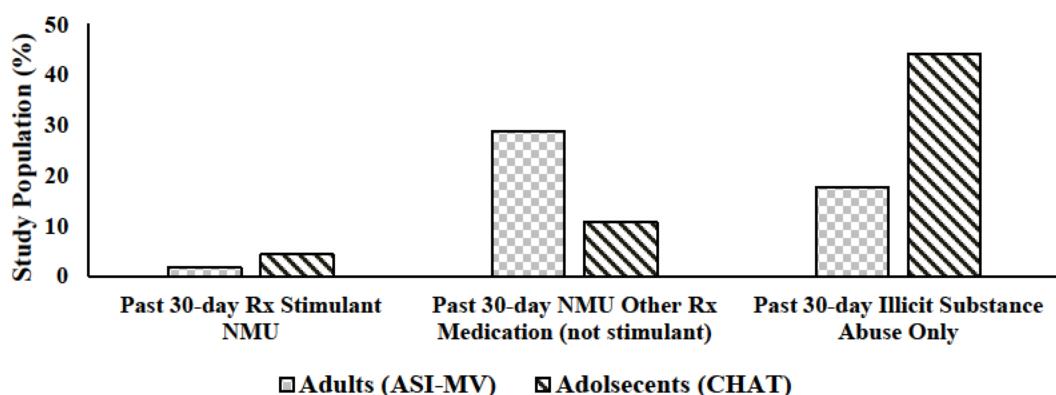
Source: Center for Behavioral Health Statistics and Quality, Substance Abuse and Mental Health Services Administration, Treatment Episode Data Set (TEDS). Data received through 11.21.18. Available at: (<https://www.samhsa.gov/data/sites/default/files/cbhsq-reports/TEDS-2017.pdf>). (accessed August 13, 2020).

NAVIPPRO® sentinel programs (e.g., ASI-MV® and CHAT®) provided an additional data source to evaluate NMU of prescription stimulants among people seeking treatment or being assessed for SUDs. However, it is important to note that the study populations drawn from individuals entering treatment facilities are dynamic and nonrepresentative, thus trends must be interpreted with caution. Results from AR19.MA003 suggested 1.7% of adults (ASI-MV®) and 4.3% of adolescents (CHAT®) reported NMU of prescription stimulants in the past 30 days (**Figure 35**). Adults (**Figure 36**) and adolescents (**Figure 37**) reported past 30-day NMU of prescription amphetamines approximately twice as frequently as prescription methylphenidates. After controlling for the number of prescriptions dispensed, NMU in the past 30 days of any prescription amphetamines, among adults, was 3.21 (95% CI: 3.13 to 3.28) cases per 100,000 prescriptions dispensed as compared to 2.62 (95% CI: 2.52 to 2.71) cases per 100,000 prescriptions dispensed for any prescription methylphenidates (**Figure 36**). NMU in the past 30 days of prescription amphetamine IR products, among adults, was 4.99 (95% CI: 4.85 to 5.14) cases per 100,000 prescriptions dispensed, while NMU in the past 30 days of prescription amphetamine ER products was 2.76 (95% CI: 2.67 to 2.85) cases per 100,000 prescriptions dispensed.

³⁰ Treatment Episode Data Set (TEDS) 2017: Admissions to and Discharges from Publicly-Funded Substance Use Treatment. Available at: <https://www.samhsa.gov/data/sites/default/files/cbhsq-reports/TEDS-2017.pdf>. (accessed August 13, 2020).

After controlling for the number of prescriptions dispensed, NMU of any prescription amphetamine in the past 30 days, among adolescents, was 0.53 (95% CI: 0.49 to 0.57) cases per 100,000 prescriptions dispensed as compared to 0.51 (95% CI: 0.46 to 0.56) cases per 100,000 prescriptions dispensed for any prescription methylphenidate (**Figure 37**). NMU in the past 30 days of prescription amphetamine IR products was 0.59 (95% CI: 0.52 to 0.65) cases per 100,000 prescriptions dispensed, which was similar to NMU in the past 30 days of prescription amphetamine ER products which was 0.65 (95% CI: 0.60 to 0.71) cases per 100,000 prescriptions dispensed.

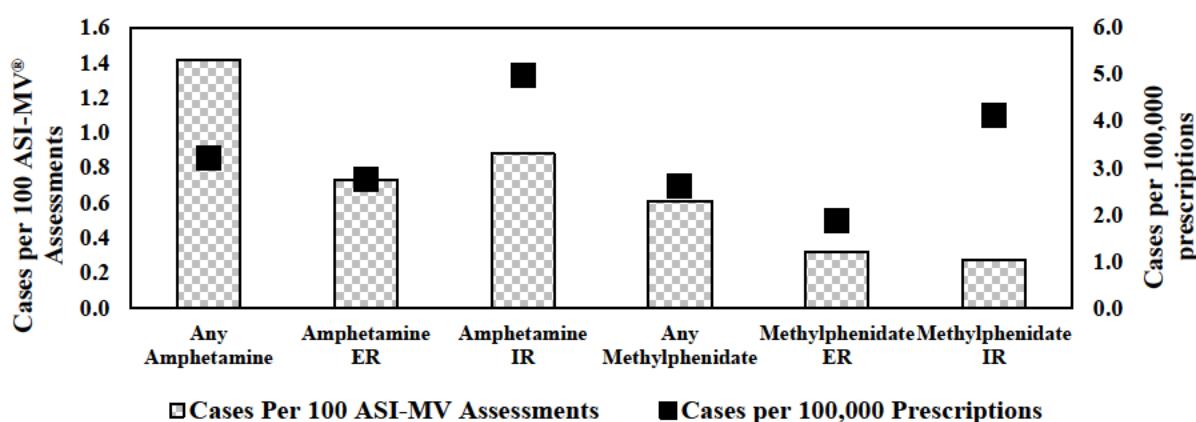
Figure 35. NMU of prescription drugs or illicit substances in the past 30 days among adult (ASI-MV®) and adolescent (CHAT®) respondents between January 1, 2010 to September 30, 2017, AR19.MA003 Survey



ASI-MV®, Addiction Severity Index-Multimedia Version; CHAT®, Comprehensive Health Assessment for Teens; NMU, nonmedical use; Rx, prescription.

Source: FDA-generated figure. Analysis of Prescription Stimulants in ASI-MV® and CHAT® (AR19.MA003). Results from Figure 1. ASI-MV® subpopulations of interest (01/01/2010 – 09/30/2017) and Figure 29. CHAT® subpopulations of interest (01/01/2010 – 09/30/2017).

Figure 36. Rates of NMU of prescription stimulants in the past 30 days among adult (ASI-MV®) respondents aged 18 years or older between January 1, 2010 to September 30, 2017, AR19.MA003 Survey



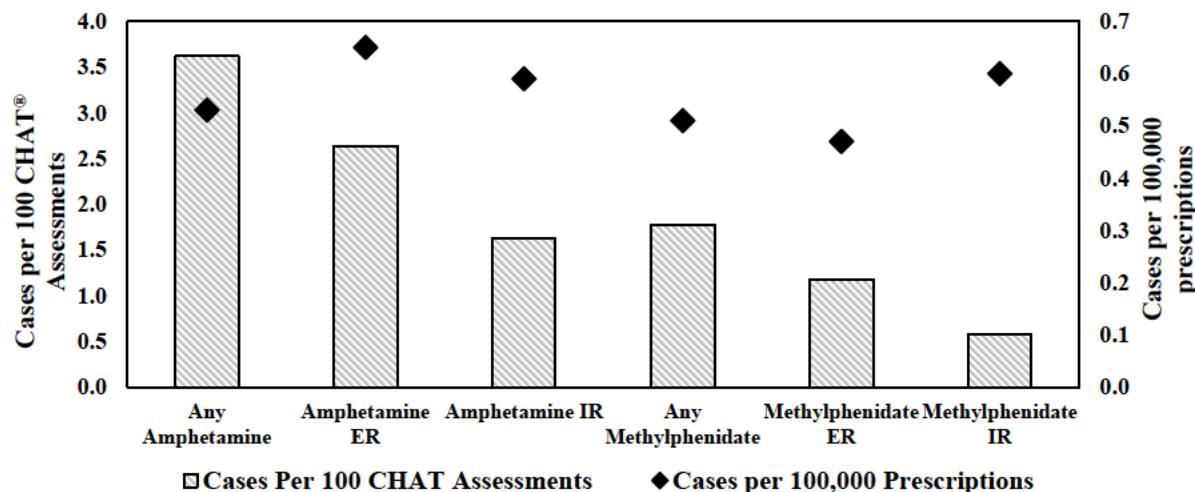
ASI-MV®, Addiction Severity Index-Multimedia Version; ER, extended-release; IR, immediate-release; NMU, nonmedical use.

Note: These data are derived from IQVIA and include only prescription dispensed in states that contributed data to the ASI-MV® network during the study period (01/01/2010 – 09/30/2017).

Note: The stimulant category 'any methylphenidate' includes both methylphenidate and dexmethylphenidate stimulant categories.

Source: FDA-generated figure. Analysis of Prescription Stimulants in ASI-MV® and CHAT® (AR19.MA003). Results from Table 5. Rates of prescription stimulant NMU (by all adults in the ASI-MV® network): cases per 100 ASI-MV® assessments, and cases per 100,000 such prescriptions dispensed in ASI-MV® network states (01/01/2010 – 09/30/2017).

Figure 37. Rates of NMU of prescription stimulants in the past 30 days among adolescent (CHAT®) respondents aged 18 years or younger between January 1, 2010 to September 30, 2017, AR19.MA003 Study



CHAT®, Comprehensive Health Assessment for Teens; ER, extended-release; IR, immediate-release; NMU, nonmedical use.

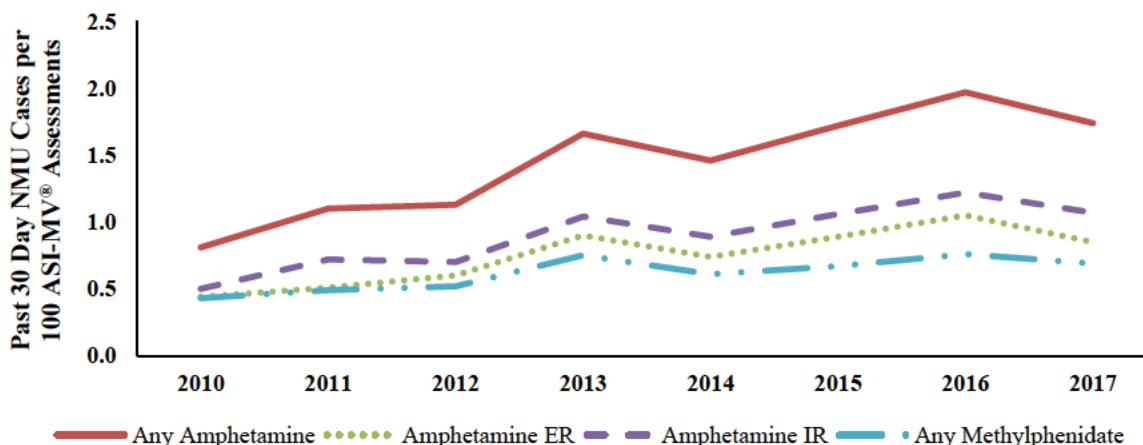
Note: These data are derived from IQVIA and include only prescription dispensed in states that contributed data to the CHAT® network during the study period (01/01/2010 – 09/30/2017).

Note: The stimulant category ‘any methylphenidate’ includes both methylphenidate and dextroamphetamine stimulant categories.

Source: FDA-generated figure. Analysis of Prescription Stimulants in ASI-MV® and CHAT® (AR19.MA003). Results from Table 19. Rates of prescription stimulant NMU (by all adolescents in the CHAT® network): cases per 100 CHAT® assessments, and cases per 100,000 such prescriptions dispensed in CHAT® network states (01/01/2010 – 09/30/2017).

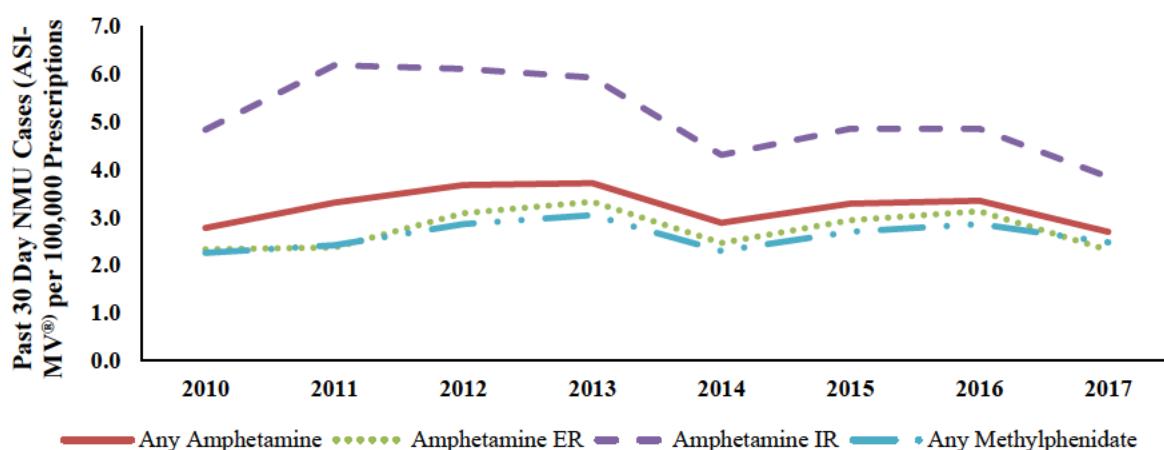
Among adult respondents included in AR19.MA003, yearly rates of NMU in the past 30 days for any prescription amphetamine increased from approximately 0.8 cases per 100 ASI-MV® assessments in 2010 to 1.7 cases per 100 ASI-MV® assessments in 2017 (Figure 38), with similar rates of NMU in the past 30 days observed between IR and ER amphetamine products. A similar trend was observed for NMU in the past 30 days of any prescription methylphenidate, where yearly rates increased from approximately 0.4 cases per 100 ASI-MV® assessments in 2010 to 0.7 cases per 100 ASI-MV® assessments in 2017 (Figure 38). However, after controlling for the number of prescriptions dispensed, yearly rates of NMU of any prescription amphetamine or methylphenidate in the past 30 days appeared to be relatively constant between 2010 and 2017 (Figure 39). Among adolescent respondents included in AR19.MA003, yearly rates of NMU in the past 30 days of any prescription amphetamine followed an inverted U-shape between 2010 and 2017. Yearly rates of NMU in the past 30 days for any prescription amphetamine were approximately 2.6 cases per 100 CHAT® assessments in 2010, peaking at 4.4 cases per 100 CHAT® assessments in 2012, followed by a steady decrease to 2.0 cases per 100 CHAT® assessments in 2017 (Figure 40). During the same time period rates of NMU in the past 30 days of any prescription methylphenidate steadily decreased from 2.9 cases per 100 CHAT® assessments in 2010 to 0.9 cases per 100 CHAT® assessments in 2017 (Figure 40). After controlling for the number of prescriptions dispensed, yearly rates of NMU in the past 30 days of any prescription amphetamine and methylphenidate peaked in 2012, followed by a steady decrease through 2017 (Figure 41).

Figure 38. Yearly rates of NMU of selected prescription stimulants in the past 30 days per 100 ASI-MV® assessments among respondents aged 18 years or older between January 1, 2010 to September 30, 2017, AR19.MA003 Survey



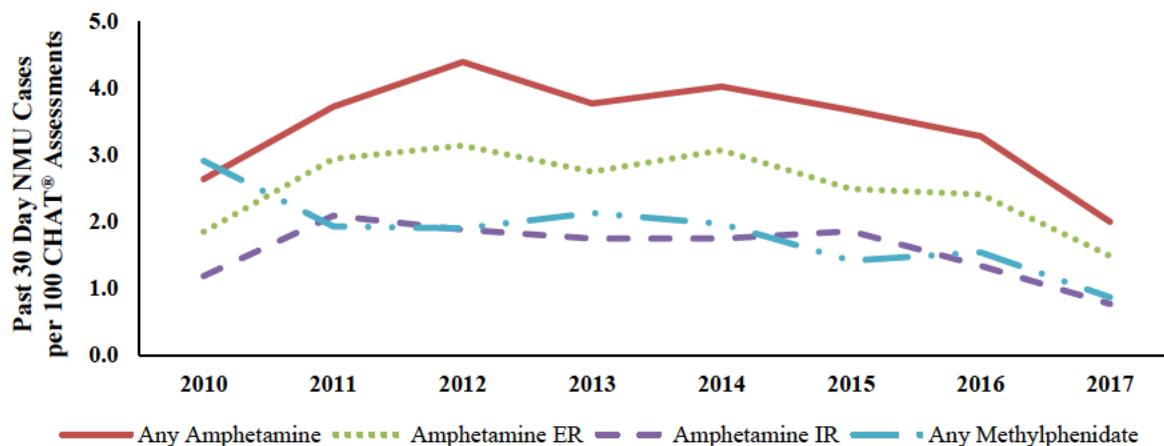
ASI-MV®, Addiction Severity Index Multimedia Version; ER, extended-release; IR, immediate-release; NMU, nonmedical use.
Source: FDA-generated figure. Analysis of Prescription Stimulants in ASI-MV® and CHAT® (AR19.MA003). Results from Appendix 9.2. Number of Patients That Reported Stimulant Nonmedical Use per 100 ASI-MV® Assessments among the Total ASI-MV® Network, by Year (01/01/2010 – 09/30/2017).

Figure 39. Yearly rates of NMU of selected prescription stimulants the past 30 days per 100,000 prescriptions dispensed, among ASI-MV® respondents aged 18 years or older between January 1, 2010 to September 30, 2017, AR19.MA003 Survey



ASI-MV®, Addiction Severity Index Multimedia Version; ER, extended-release; IR, immediate-release; NMU, nonmedical use.
Source: FDA-generated figure. Analysis of Prescription Stimulants in ASI-MV® and CHAT® (AR19.MA003). Results from Appendix 9.3. Number of Patients That Reported Stimulant Nonmedical Use per 100,000 Prescriptions Dispensed among the ASI-MV® Network, by Year (01/01/2010 – 09/30/2017).

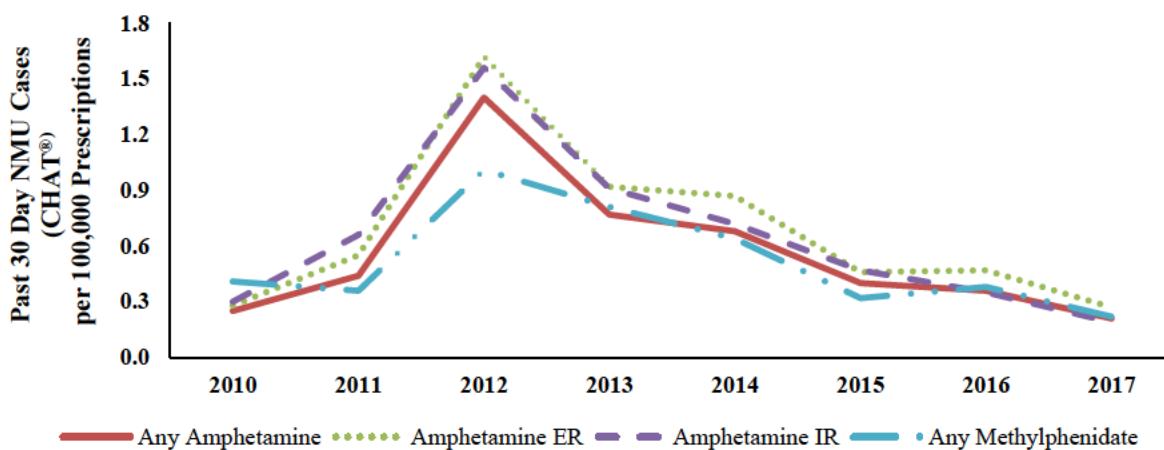
Figure 40. Yearly rates of NMU of selected prescription stimulants in the past 30 days per 100 CHAT® assessments among respondents aged 18 years or younger between January 1, 2010 to September 30, 2017, AR19.MA003 Survey



CHAT®, Comprehensive Health Assessment for Teens; ER, extended-release; IR, immediate-release; NMU, nonmedical use.

Source: FDA-generated figure. Analysis of Prescription Stimulants in ASI-MV® and CHAT® (AR19.MA003). Results from Appendix 9.8. Number of Patients That Reported Stimulant Nonmedical Use per 100 Assessments among the Total CHAT® Network, by Year (01/01/2010 – 09/30/2017).

Figure 41. Yearly rates of NMU of selected prescription stimulants the past 30 days per 100,000 prescriptions dispensed, among CHAT® respondents aged 18 years or younger between January 1, 2010 to September 30, 2017, AR19.MA003 Survey



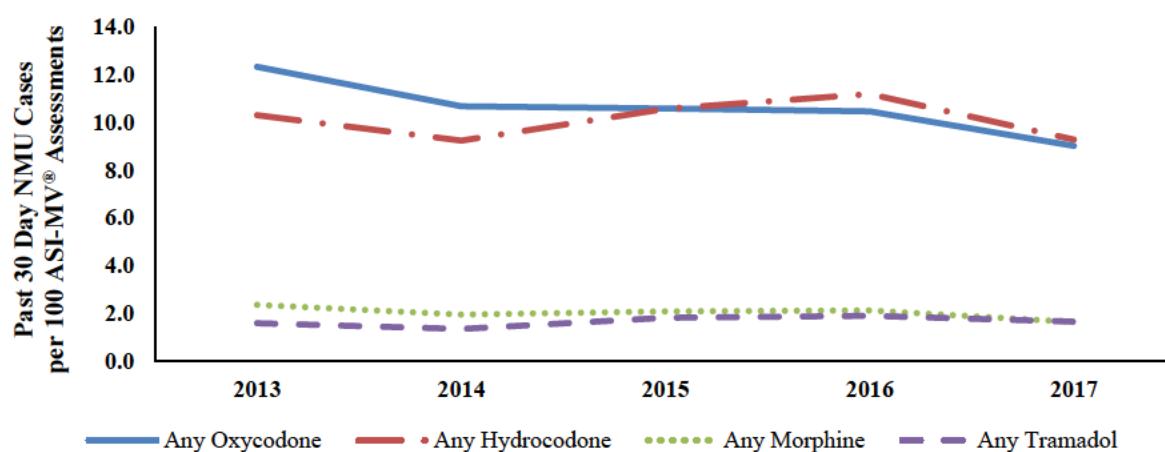
CHAT®, Comprehensive Health Assessment for Teens; ER, extended-release; IR, immediate-release; NMU, nonmedical use.

Source: FDA-generated figure. Analysis of Prescription Stimulants in ASI-MV® and CHAT® (AR19.MA003). Results from Appendix 9.9. Number of Patients That Reported Stimulant Nonmedical Use per 100,000 Prescriptions Dispensed among the CHAT® Network, by Year (01/01/2010 – 09/30/2017).

To put the results above in context, yearly rates of NMU in the past 30 days between 2013 and 2017 for selected prescription opioid analgesics is summarized in **Figure 42**. Briefly, these data suggested in 2017 the rate of NMU in the past 30 days of oxycodone and hydrocodone per 100 ASI-MV® assessments was approximately an order of magnitude greater than the rate of NMU in the past 30 days of any prescription amphetamine per 100 ASI-MV® assessments reported in AR19.MA003; while the rate of NMU in the

past 30 days for morphine and tramadol per 100 ASI-MV® assessments was similar to the rate of NMU in the past 30 days for any amphetamine per 100 ASI-MV® assessments reported in AR19.MA003.

Figure 42. Yearly rates of NMU of selected prescription opioid analgesics in the past 30 days per 100 ASI-MV® assessments among respondents aged 18 years or older between 2013 to 2017, FDA's National Addictions Vigilance Intervention and Prevention Program, ASI-MV® Reports



ASI-MV®, Addiction Severity Index Multimedia Version; FDA, United States Food and Drug Administration; NMU, nonmedical use. Source: FDA-generated figure. The Addiction Severity Index - Multimedia Index (ASI-MV®), a data source of the NAVIPPRO® surveillance system, Inflexxion, Inc., an IBH Company, Irvine, CA. Results from Spring 2020 Trend Report provided to the FDA.

3.2.2 Route of Administration in NMU of Prescription and Illicit Stimulants

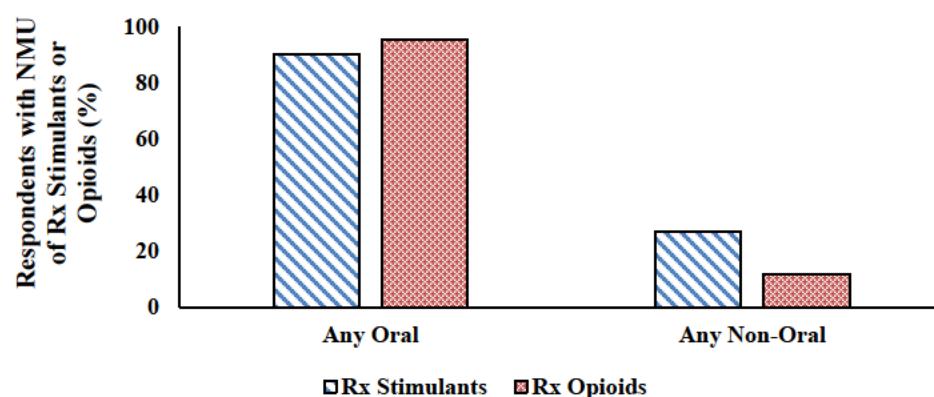
3.2.2.1 Route of Administration Reported in General U.S. Population Studies

Among respondents with a lifetime history of NMU of prescription stimulants included in the Applicant-submitted general population survey, AR19.MA004, 90.4% reported lifetime NMU of a prescription stimulant via an oral route of administration and 27.2% reported lifetime NMU of a prescription stimulant via a non-oral route of administration (Figure 43). The most common non-oral route reported across the lifetime of respondents was snorting (24.7%), followed by smoking (3.8%) and injecting (3.5%) (Figure 44). Similar to prescription stimulants, AR19.MA004 respondents predominantly reported NMU of any prescription opioid analgesic via an oral route of administration; however, NMU of any prescription opioid analgesic via non-oral routes of administration was lower compared to NMU of prescription stimulants. The differences observed in overall non-oral NMU were driven by differences in snorting, which was reported by 24.7% of respondents with NMU of any prescription stimulant compared to 11.8% of respondents with NMU of any prescription opioid analgesic. NMU via other non-oral routes (e.g., smoking, injecting) was similar between those with NMU of prescription stimulants and prescription opioid analgesics. *Note: The comparison of routes by prescription stimulant vs opioid analgesic class can be misleading, as the opioid analgesic market largely comprises low-dose IR products in combination with non-opioid analgesics such as acetaminophen.³¹ These combination products have relatively low levels of non-oral use, compared to less frequently prescribed single-entity products available in higher dosage strengths. Routes of administration vary greatly by opioid analgesic drug (active ingredient), as*

³¹ 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. Figure 1. Estimated number of dispensed prescriptions for all opioid analgesics (grey bar) and the top 5 (solid lines), from U.S. retail pharmacies, 2009-2018. Page 20. Available at: <https://www.fda.gov/media/134128/download> (accessed September 14, 2020).

described, below, as well as whether the product is single-entity or combined with a non-opioid analgesic (e.g., acetaminophen).³²

Figure 43. Routes of administration for NMU of prescription stimulants and opioid analgesics, among people aged 18 to 49 years, AR19.MA004, an online survey of the general U.S. population conducted by the internet panel company YouGov



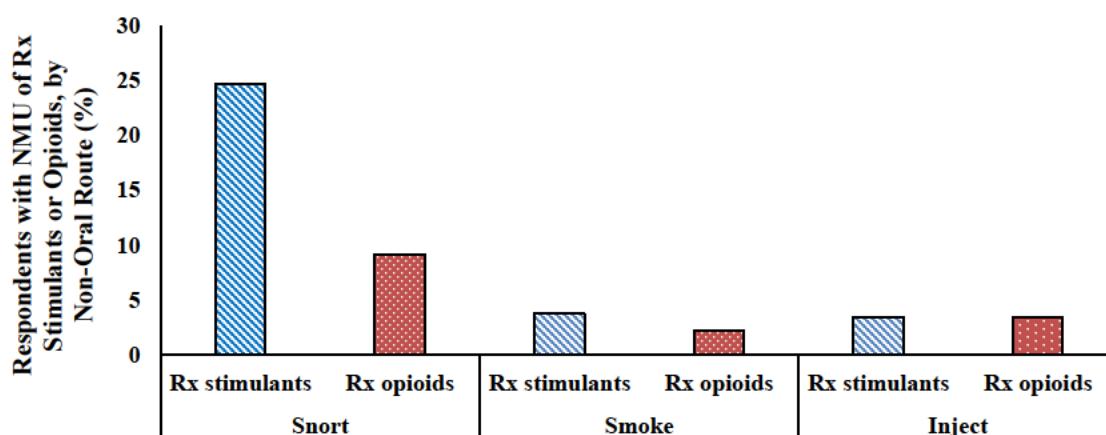
NMU, nonmedical use; Rx, prescription; U.S., United States.

Note: Any oral refers to swallowed whole, chewed then swallowed, or dissolved in liquid then swallowed.

Note: Any non-oral refers to snorting, smoking, or injecting.

Source: FDA-generated figure. Nonmedical Use of Prescription Medications among the General Population (AR19.MA004). Results from Table 15. Routes of administration for NMU of prescription stimulants.

Figure 44. Non-oral routes of administration for NMU of prescription stimulants and opioids analgesic, among people aged 18 to 49 years, AR19.MA004, an online survey of the general U.S. population conducted by the internet panel company YouGov



NMU, nonmedical use; Rx, prescription; U.S. United States.

Source: FDA-generated figure. Nonmedical Use of Prescription Medications among the General Population (AR19.MA004). Results from Table 15. Routes of administration for NMU of prescription stimulants.

³² Cassidy TA, Oyedele N, Mickle TC, Guenther S, and Budman SH. Patterns of abuse and routes of administration for immediate-release hydrocodone combination products. *Pharmacoepidemiol Drug Saf*. 2017; 26: 1071–1082.

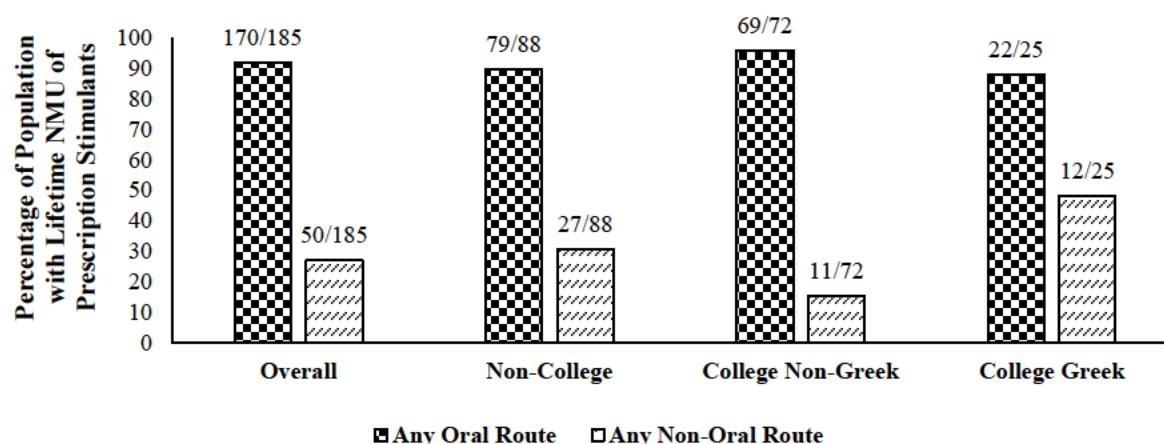
Supplemental Figure 1A. Available at: <https://doi.org/10.1002/pds.4249>

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5637894/bin/PDS-26-1071-s001.pdf> (accessed September 14, 2020).

Among respondents to a separate Applicant-submitted survey, AR19.MA012, which included individuals between the ages of 18 and 26 years with a lifetime history of NMU of prescription stimulants, 91.9% reported lifetime NMU of a prescription stimulant via an oral route of administration and 27.0% reported lifetime NMU of a prescription stimulant via a non-oral route of administration (**Figure 45**). When further stratified by college enrollment status, college students who participated in Greek life (i.e., fraternities, sororities) had the lowest percentage of respondents that reported prescription stimulant NMU via any oral route (88.0%) and highest percentage of respondents that reported prescription stimulant NMU via any non-oral route (48.0%). College students who did not participate in Greek life had the highest percentage of respondents that reported prescription stimulant NMU via any oral route (95.8%) and lowest percentage of respondents that reported prescription stimulant NMU via any non-oral route (15.2%). As a comparison, 89.8% of similarly aged respondents not enrolled in college reported prescription stimulant NMU via any oral route and 30.7% reported prescription stimulant NMU via any non-oral route.

Among 27 youth respondents between the ages of 10 and 17 years who reported non-oral use of prescription stimulants in a cross-sectional survey conducted in three U.S. states in 2018 (AR19.MA010), only 2 respondents reported injection, 8 reported smoking, and 19 reported snorting. About half of respondents who reported non-oral use also reported oral use of prescription stimulants (n=14) (**Table 18**).

Figure 45. Route of administration for lifetime NMU of prescription stimulants, by college enrollment status, AR19.MA012, an online survey of the general U.S. population aged 18 to 26 years conducted by the internet panel company YouGov



NMU, nonmedical use; U.S., United States.

Note: Responses are not mutually exclusive and do not necessarily add to 100%.

Note: The fractions above each bar show the number of respondents with NMU of prescription stimulants over the total number of respondents in each category.

Note: Greek refers to participation in fraternities or sororities.

Note: Any oral route refers to swallowed whole, chewed in mouth then swallowed, or dissolved in liquid then swallowed.

Note: Any non-oral route refers to snorting, smoking, or injecting.

Source: FDA-generated figure. Nonmedical Use of Prescription Medications in College Students Involved in Greek Life (AR19.MA012). Results from Table 15. Routes of administration for prescription stimulant NMU, by enrollment in college and Greek life participation.

Table 18. Patterns of non-oral use of prescription stimulants in a sample of youth ages 10 to 17 from three U.S. states* in 2018, AR19.MA010, an anonymous in-person interviewer-facilitated survey of general population youth that reported non-oral use of prescription stimulants, conducted by the Substance Abuse Training Center in Public Health at the University of Florida

Patterns of Non-oral Use	N	%**
Oral and Snort	10	37
Snort Only	7	26
Smoke Only	4	15
Oral and Smoke	2	7
Snort and Smoke	2	7
Oral and Injection	2	7

U.S., United States.

Note: ** The three states included in this study were California, Texas, and Florida.

Note: *** The percentage is calculated out of the total study population reporting non-oral use of prescription stimulants (N=27).

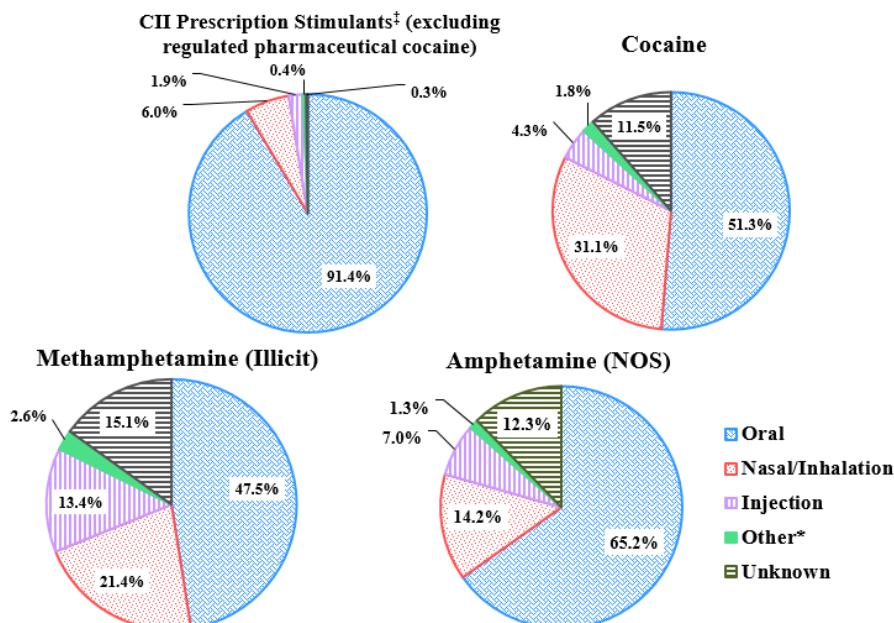
Source: FDA-generated table from information in the Study of Non-oral Administration of Prescription Stimulants (SNAPS) report Table 17A (AR19.MA010) Characteristics of stimulant non-oral users.

3.2.2.2 Route of Administration Among People Seeking Advice or Healthcare

From 2001 through 2018, over 91% of the routes of exposure mentioned in single-substance³³ NPDS exposure cases involving NMU of CII prescription stimulants were oral, while 6.0% of routes were nasal/inhalation and 1.9% were injection (**Figure 46**). For single-substance NMU cases involving cocaine and illicit methamphetamine, approximately 50% of exposure routes were oral, while over 33% of exposure routes were either nasal/inhalation or injection. More than 65% of the routes mentioned in single-substance NMU NPDS exposure cases involving NMU of unspecified amphetamines were oral. Trends in exposure routes documented in single-substance NMU NPDS cases remained stable across the eighteen-year period.

³³ In NPDS data, the route of administration is not captured specifically for each substance reported in a multi-substance exposure case, and multiple routes can be reported for a single substance. Therefore, we restricted the data to cases involving only a single substance, and for these cases, we counted each route mentioned by the caller separately. As the totals for each individual route may exceed the total number of exposure cases for that substance, for analyses involving only CII prescription stimulants (analyses that do not include comparisons to select prescription opioid analgesics), route of exposure percentages were calculated out of the total route mentions.

Figure 46. Routes of exposure involved in NMU of prescription and illicit stimulants in National Poison Data System single-substance exposure cases, by stimulant category, 2001 to 2018



CII, Schedule II; NMU, nonmedical use; NOS, not otherwise specified.

Note: '[‡]' indicates CII stimulants only. Prescription stimulants include amphetamine, dextroamphetamine, amphetamine mixed salts, lisdexamfetamine, methylphenidate, dextroamphetamine, and methamphetamine. Regulated pharmaceutical cocaine and stimulants indicated for weight-loss (e.g., phentermine) are not included.

Note: Reports of regulated pharmaceutical and illicit cocaine exposures are considered together.

Note: Amphetamine exposures not referencing a specific prescription or illicit product are considered "Amphetamine (NOS)."

Note: NMU consists of "Intentional – Misuse" and "Intentional – Abuse" exposures.

Note: Includes single-substance prescription and illicit stimulant NMU exposure cases.

Note: Excludes prescription and illicit stimulant exposure cases with "Intentional - Suspected Suicide" or "Intentional - Unknown" reasons.

Note: '*' Route of exposure "Other" includes aspiration, bite/sting, dermal, ocular, other, otic, rectal, and vaginal.

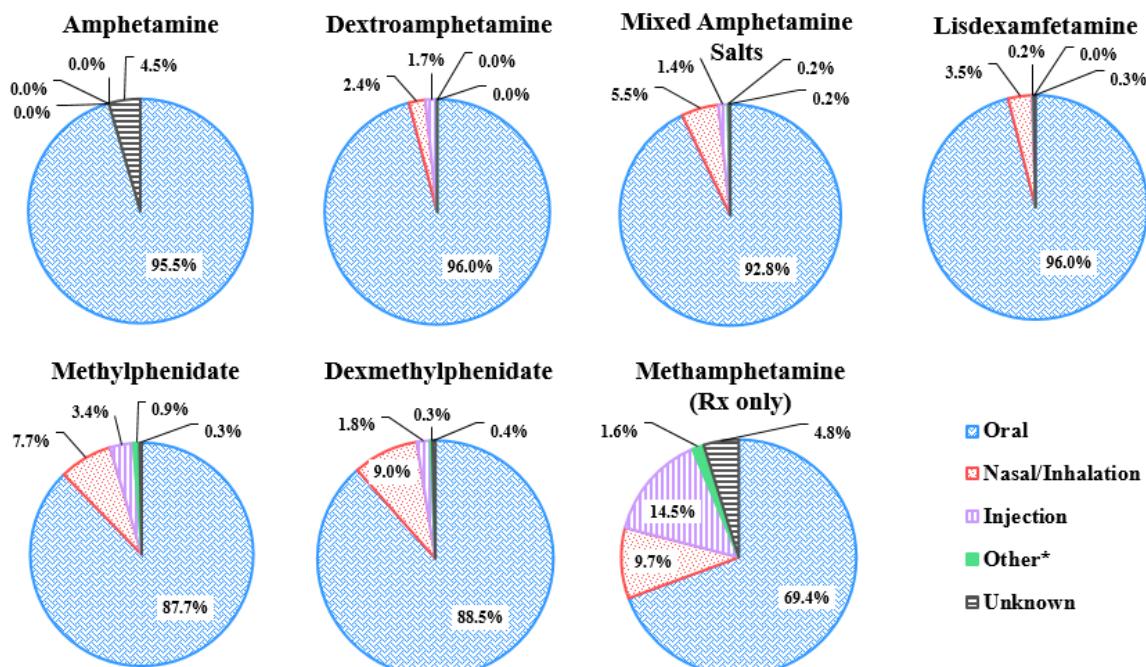
Note: Children 5 years and younger are not included.

Note: Percentages are calculated using total route of NMU mentions for each stimulant category.

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

Figure 47 shows the various routes of exposure documented in NPDS exposure cases that involved single-substance NMU of CII prescription stimulants, stratified by API. For all CII prescription stimulant APIs except prescription methamphetamine, 88% to 96% of the route mentions were oral. An oral route was mentioned more often in cases involving amphetamine-containing prescription stimulant APIs (92% to 96% of total route mentions) than in cases involving methylphenidate-containing prescription stimulant APIs (87% to 89% of total route mentions), and a nasal/inhalation or injection route was mentioned less often in cases involving amphetamine-containing prescription stimulant APIs (0% to 6% and 0% to 1.7% of total route mentions, respectively) than in cases involving methylphenidate-containing prescription stimulant APIs (7% to 9% and 1% to 4% of total route mentions, respectively). In comparison, almost 25% of the total route mentions in single-substance NPDS exposure cases involving NMU of prescription methamphetamine were nasal/inhalation or injection.

Figure 47. Routes of exposure involved in NMU of CII prescription stimulants in National Poison Data System single-substance exposure cases, by API, 2001 to 2018



API, active pharmaceutical ingredient; NMU, nonmedical use; NOS, not otherwise specified; Rx, prescription.

Note: Schedule II stimulants only.

Note: Reports of regulated pharmaceutical and illicit cocaine exposures are considered together and are therefore excluded.

Note: Amphetamine exposures not referencing a specific prescription or illicit product are considered "Amphetamine (NOS)," and are also excluded.

Note: NMU consists of "Intentional – Misuse" and "Intentional – Abuse" exposures.

Note: Includes single-substance prescription stimulant NMU exposure cases only.

Note: Excludes prescription stimulant exposure cases with "Intentional - Suspected Suicide" and "Intentional - Unknown" reasons.

Note: * Route of exposure "Other" includes aspiration, bite/sting, dermal, ocular, other, otic, rectal, and vaginal.

Note: Children 5 years and younger are not included.

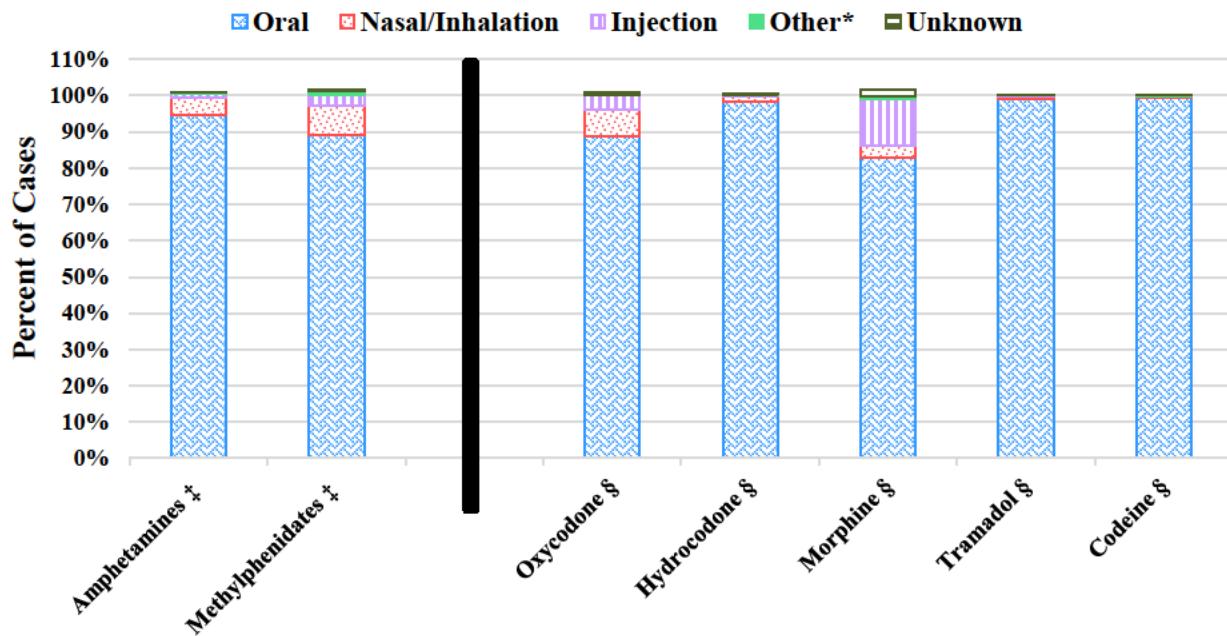
Note: Percentages are calculated using total route of misuse/abuse mentions for each stimulant category.

Note: The total number of routes for each API is as follows: Amphetamine (N = 22), Dextroamphetamine (N = 421), Mixed Amphetamine Salts (N = 11,526), Lisdexamfetamine (N = 2,542), Methylphenidate (N = 7,071), Dexmethylphenidate (N = 713), and Methamphetamine (Rx only) (N = 62).

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

For comparison, we included exposure routes documented in single-substance NPDS exposure cases involving NMU of selected prescription opioid analgesic APIs and formulations. For prescription amphetamine and methylphenidate APIs from 2001 through 2018 and for prescription oxycodone, hydrocodone, morphine, tramadol, and codeine APIs from 2014 through 2018, the vast majority (82% to over 99%) of exposures mentioned in single-substance NMU NPDS exposure cases were oral (**Figure 48**).

Figure 48. National Poison Data System single-substance exposure cases involving NMU of prescription stimulants and opioid analgesics, by route of exposure



CII, Schedule II; NMU, nonmedical use.

Note: '‡' indicates CII stimulants only. Prescription stimulants include amphetamine, dextroamphetamine, amphetamine mixed salts, lisdexamfetamine, methylphenidate, dexmethylphenidate, and methamphetamine. Regulated pharmaceutical cocaine and stimulants indicated for weight-loss (e.g., phentermine) are not included.

Note: Includes single-substance prescription stimulant and single-substance prescription opioid analgesic exposure cases only.

Note: NMU consists of "Intentional – Misuse" and "Intentional – Abuse" exposures.

Note: Excludes prescription stimulant and opioid analgesic exposure cases with "Intentional - Suspected Suicide" and "Intentional - Unknown" reasons.

Note: Routes are represented as percentage of exposure cases reporting a specific route over all the single-substance exposure cases for the stimulant or opioid analgesic. One exposure case may be associated with more than one exposure route, thus, the total % for each column may exceed 100%.

Note: Children 5 years and younger are excluded from the prescription stimulant exposure cases.

Note: '*' Route of exposure "Other" includes aspiration, bite/sting, dermal, ocular, other, otic, rectal, and vaginal.

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

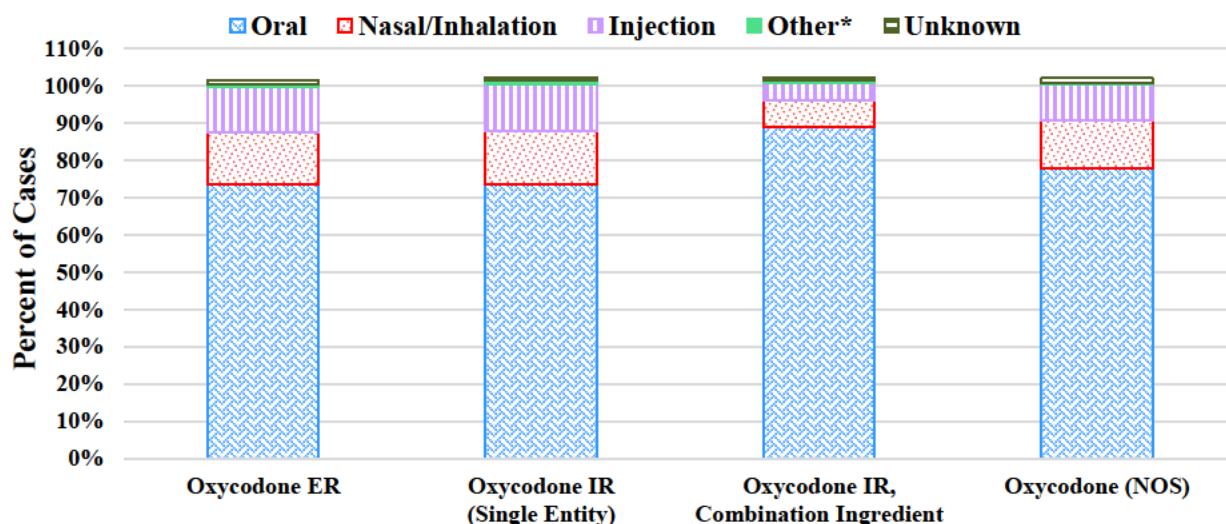
Note: '‡' indicates the time period of 2001-2018.

Source: 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).

Note: '§' indicates the time period of 2014-2018.

As shown in **Figure 48, above**, and noted in **Section 3.2.2.1** there was wider variation in the route of exposure documented in NPDS cases involving the selected prescription opioid analgesic APIs that can make comparisons of routes between prescription stimulant and opioid analgesic classes misleading. From 2012 through 2017 among people >12 years of age, an oral exposure route was documented in almost 89% of NPDS cases involving intentional – abuse of IR oxycodone combination products, while nasal/inhalation was documented in over 7% of cases involving intentional – abuse and injection was documented in almost 5% of cases involving intentional – abuse (**Figure 49**). In comparison, for both single entity, IR oxycodone products and ER oxycodone products, an oral route of exposure was documented in less than 75% of NPDS exposure cases involving intentional – abuse, while nasal/inhalation was documented in over 14% of cases involving intentional – abuse and injection was documented in over 12% of cases involving intentional – abuse.

Figure 49. National Poison Data System single-substance exposure cases involving intentional – abuse of prescription oxycodone, by route of exposure, 2012 to 2017



IR, immediate-release, ER, extended-release; NOS, not otherwise specified.

Note: Includes single-substance “Intentional – Abuse” exposure cases only. Excludes cases with “Intentional - Misuse,” “Intentional - Suspected Suicide,” and “Intentional - Unknown” reasons.

Note: Routes are represented as percentage of exposure cases reporting a specific route over all of the single-substance exposure cases for the opioid analgesic. One exposure case may be associated with more than one exposure route, thus, the total % for each column may exceed 100%.

Note: Children 11 years and younger are not included.

Note: “*” Route of exposure “Other” includes aspiration, bite/sting, dermal, ocular, other, otic, rectal, and vaginal.

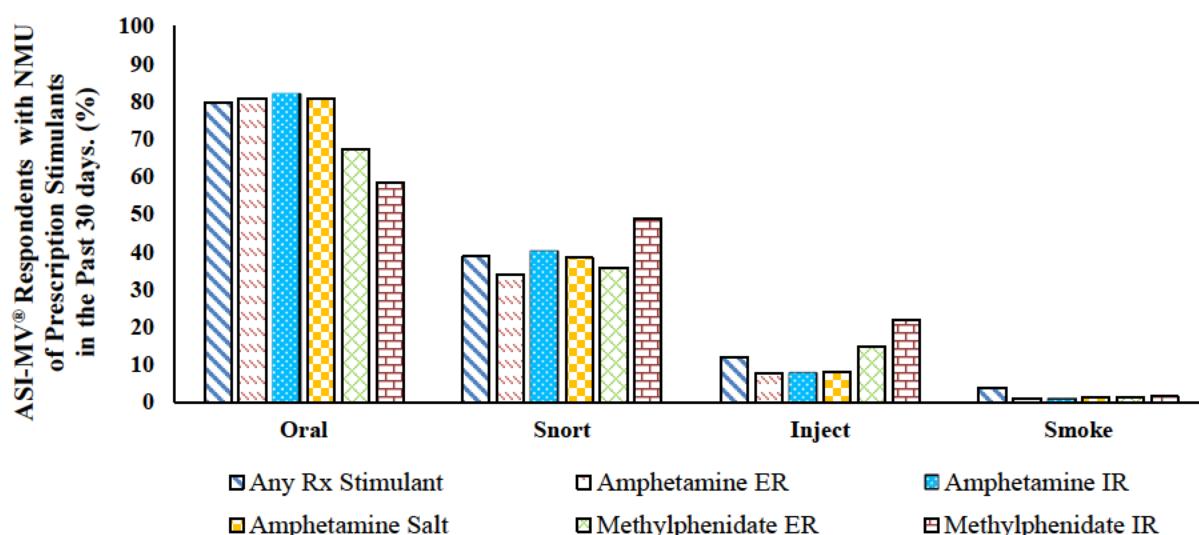
Source: Joint Meeting of Anesthetic and Analgesic Drug Products Advisory Committee and Drug Safety and Risk Management Advisory Committee. January 15, 2020. Epidemiology Review: Misuse and Abuse of Oxycodone and Other Opioids in the United States. Table 5. AAPCC NPDPS, 2012-2017: Percentage (%) of single-substance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

3.2.2.3 Route of Administration Reported in Enriched Populations

Summarized in **Figure 50**, adult (ASI-MV®) respondents entering treatment or being assessed for SUDs (AR19.MA003), reported the frequency of NMU in the past 30 days of selected prescription stimulant categories, by route of administration. Among respondents with NMU in the past 30 days of any prescription stimulant, 79.7% reported NMU via an oral route of administration. Respondents also reported NMU in the past 30 days of any prescription stimulant via non-oral routes of administration, including snorting (38.8%), injecting (12.0%), and smoking (3.8%).

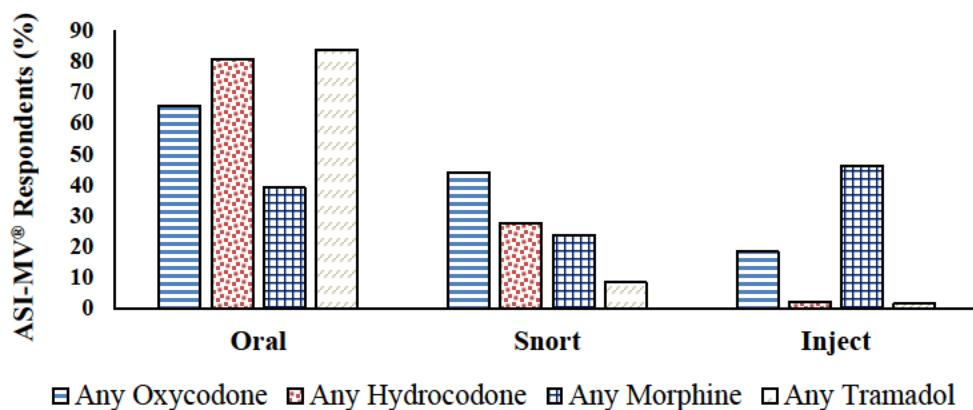
In this study, past 30-day oral NMU of any amphetamine IR product was more commonly reported than of any prescription methylphenidate IR product, while past 30-day NMU, via snorting, of any prescription methylphenidate IR product was more commonly reported than any prescription amphetamine IR product (**Figure 50**). Only 7.9% of respondents with past-30-day NMU of a prescription amphetamine IR product reported injecting as a route of administration compared to 21.9% of respondents with past-30-day NMU of a prescription methylphenidate IR product. For comparison, between 2017 and 2018, similar past-30-day route of administration patterns were reported for NMU of selected opioid analgesics (e.g., oxycodone, hydrocodone), with the greatest frequency of NMU reported via oral routes, followed by snorting and injecting (**Figure 51**). However, it is important to note that wide variation in the route of administration reported was observed across the selected opioid analgesic APIs and formulations, most likely resulting from high utilization of low-dose immediate-release combination products (e.g., hydrocodone/acetaminophen, oxycodone/acetaminophen) that have less frequent reports of non-oral use as well as higher dosage strength single-entity and extended-release products with more frequent non-oral use, as discussed in **Section 3.2.2.2, above**.

Figure 50. Routes of administration for NMU of selected prescription stimulant categories between January 1, 2010 to September 30, 2017, among ASI-MV® respondents aged 18 years or older who reported NMU of prescription stimulants in the past 30 days, AR19.MA003 Study



ASI-MV®, Addiction Severity Index Multimedia Version; ER, extended release; IR, immediate release; NMU, nonmedical use; Rx, prescription. Source: FDA-generated figure. Analysis of Prescription Stimulants in ASI-MV® and CHAT® (AR19.MA003). Results from Table 8. Routes of administration for NMU of prescription stimulants among the total ASI-MV® network (01/01/2010 – 09/30/2017).

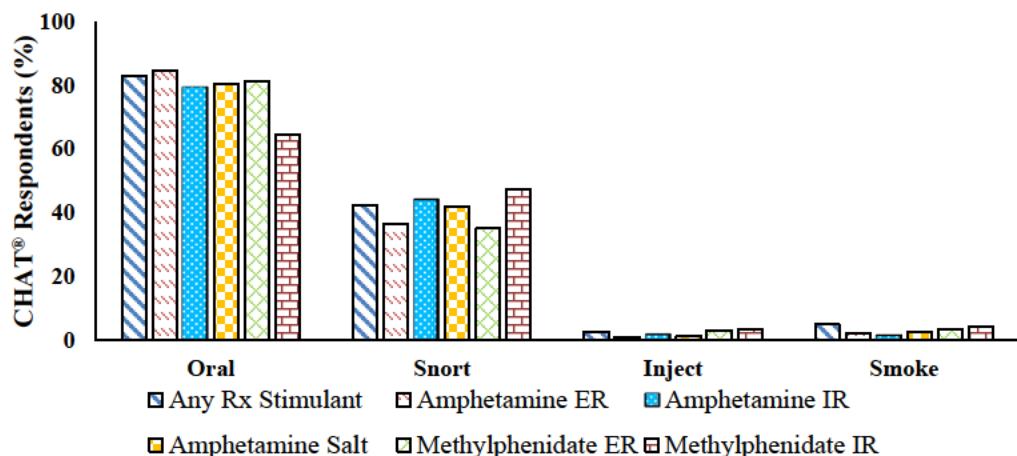
Figure 51. Routes of administration for past 30-day NMU of selected prescription opioid analgesics, among ASI-MV® respondents aged 17 years or older, 2017 to 2018, National Addictions Vigilance Intervention and Prevention Program, ASI-MV® reports provided to FDA



ASI-MV®, Addiction Severity Index Multimedia Version; FDA, United States Federal Drug Administration; NMU, nonmedical use. Source: FDA-generated figure. Internal FDA reports from the National Addictions Vigilance Intervention and Prevention Program, Addiction Severity Index-Multimedia Version.

Figure 52 summarizes data collected on the frequency of NMU in the past 30 days of selected prescription stimulant categories, by route of administration, among adolescent respondents being assessed for treatment of substance use disorders (AR19.MA003). Among respondents with NMU of any prescription stimulant in the past 30 days, 83.1% reported NMU via an oral route of administration. Respondents also commonly reported NMU via non-oral routes of administration for any prescription stimulant, including snorting (42.4%), smoking (4.8%), and injecting (2.5%). Patterns of NMU across routes of administration were largely similar between prescription amphetamines and methylphenidates.

Figure 52. Routes of administration for NMU in the past 30 days of selected prescription stimulant categories between January 1, 2010 to September 30, 2017, among CHAT® respondents aged 18 years or younger, AR19.MA003 Study



CHAT®, Comprehensive Health Assessment for Teens; ER, extended release; IR, immediate release; NMU, nonmedical use; Rx, prescription. Source: FDA-generated figure. Analysis of Prescription Stimulants in ASI-MV® and CHAT® (AR19.MA003). Results from Table 22. Routes of administration for NMU of prescription stimulants among the total CHAT® network (01/01/2010 – 09/30/2017).

Among respondents with a lifetime history of prescription stimulant NMU via a non-oral route included in the Applicant-submitted online survey, AR19.MA008, snorting was also the most common non-oral route reported (99.1%), followed by injecting (6.2%) and smoking (3.6%) (**Table 19**). Most respondents (85.3%) also reported NMU of a prescription stimulant via an oral route. Lifetime NMU, by any oral route, of prescription amphetamines and methylphenidates were reported at a similar rate (85.2% versus 82.5%, respectively), while lifetime NMU of prescription amphetamines, by any non-oral route, was reported more frequently than prescription methylphenidates (95.2% versus 58.3%, respectively).

Table 19. Reported routes used, by stimulant type, AR19.MA008, an online survey of Reddit users aged 18 years or older with a history of non-oral prescription stimulant use

Any Route of Administration for NMU Tried	Lifetime Prescription Stimulant NMU via Non-Oral Routes* (N=225)		Lifetime NMU of Prescription Amphetamines* (N=209)		Lifetime NMU of Prescription Methylphenidates* (N=103)	
	n	%	n	%	n	%
ANY ORAL ROUTE	192	85.3	178	85.2	85	82.5
Swallowed whole	185	82.2	168	80.4	78	75.7
Cut or broke into smaller pieces then swallowed	35	15.6	31	14.8	12	11.7
Chewed in mouth then swallowed	26	11.6	22	10.5	10	9.7
Dissolved in liquid then swallowed	16	7.1	16	7.7	2	1.9
ANY NON-ORAL ROUTE	225	100.0	199	95.2	60	58.3
Snorted	223	99.1	196	93.8	58	56.3
Smoked	8	3.6	6	2.9	4	3.9
Injected	14	6.2	11	5.3	4	3.9

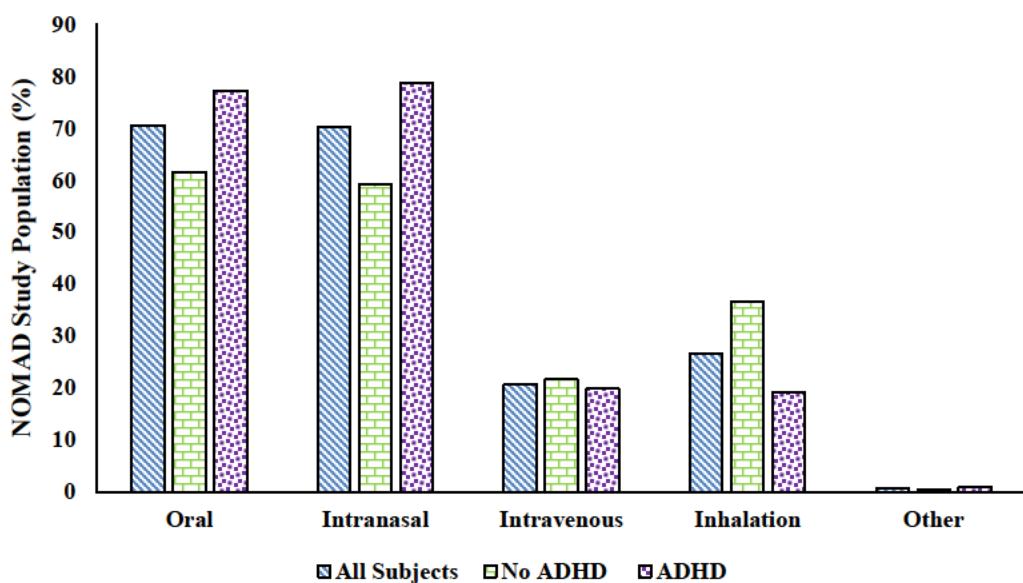
NMU, nonmedical use.

Note: ** indicates responses are not mutually exclusive and do not necessarily add to 100%.

Source: Understanding the Patterns of Prescription Medication Abuse and Progression to Non-Oral Routes of Administration (AR19.MA008). Results from Table 11. Routes of administration for prescription stimulant NMU among respondents reporting prescription stimulant NMU via non-oral routes.

Among NOMAD respondents aged 18 years or older with a history of NMU of prescription ADHD stimulants via a non-oral route, the most common routes ever used for prescription ADHD stimulants were oral (70.5%) and snorting (70.3%), followed by smoking (26.7%) and injecting (20.6%) (**Figure 53**). NOMAD respondents with ADHD were more likely to report oral and intranasal use and less likely to report inhalation when compared to respondents without ADHD. Data collected from NOMAD respondents also suggested the frequency of non-oral use of prescription amphetamines was greater than the frequency of non-oral use of prescription methylphenidates (**Table 20**).

Figure 53. Reported routes ever used for prescription ADHD stimulants, NOMAD, an online survey of adults aged 18 years or older with a history of NMU of prescription ADHD stimulants via a non-oral route



ADHD, Attention Deficit Hyperactivity Disorder; NMU, nonmedical use.

Source: FDA-generated figure. The NOMAD Non-Oral Abuse Survey: Elucidation of Pathways to Non-Oral ADHD Prescription Stimulant Abuse (NOMAD). Results from Table 14.1.2. Screening Questions.

Table 20. Specific prescription ADHD stimulant used during first non-oral NMU event, NOMAD, an online survey of adults aged 18 years or older with a history of NMU of prescription ADHD stimulants via a non-oral route

	No ADHD Dx (N=430)	ADHD Dx (N=575)	All Subjects (N=1005)
Thinking back to the first time you recall non-orally abusing a prescription ADHD stimulant, what was the name of the prescription ADHD stimulant you used?			
n			
Adderall (amphetamine) (brand or generic formulation)	430 212 (49.3%)	575 294 (51.1%)	1005 506 (50.3%)
Adderall XR (amphetamine) (brand or generic formulation)	74 (17.2%)	111 (19.3%)	185 (18.4%)
Adzenys XR-ODT (amphetamine) (brand or generic formulation)	27 (6.3%)	16 (2.8%)	43 (4.3%)
Vyvanse (lisdexamfetamine) (brand or generic formulation)	19 (4.4%)	25 (4.3%)	44 (4.4%)
Dexedrine / Zenedri (dextroamphetamine) (brand or generic formulation)	26 (6.0%)	23 (4.0%)	49 (4.9%)
Dyanavel XR (amphetamine) (brand or generic formulation)	21 (4.9%)	22 (3.8%)	43 (4.3%)
Evekeo (amphetamine) (brand or generic formulation)	14 (3.3%)	8 (1.4%)	22 (2.2%)
TOTAL AMPHETAMINE	393 (91.4%)	499 (86.8%)	892 (88.8%)
Aptensio XR (methylphenidate) (brand or generic formulation)	20 (4.7%)	12 (2.1%)	32 (3.2%)
Concerta (methylphenidate) (brand or generic formulation)	31 (7.2%)	29 (5.0%)	60 (6.0%)
Ritalin (methylphenidate) (brand or generic formulation)	71 (16.5%)	100 (17.4%)	171 (17.0%)
Ritalin LA / Ritalin SR (methylphenidate) (brand or generic formulation)	25 (5.8%)	18 (3.1%)	43 (4.3%)
Focalin (dexmethylphenidate) (brand or generic formulation)	21 (4.9%)	13 (2.3%)	34 (3.4%)
Focalin XR (dexmethylphenidate) (brand or generic formulation)	14 (3.3%)	12 (2.1%)	26 (2.6%)
Quillichew ER (methylphenidate) (brand or generic formulation)	7 (1.6%)	6 (1.0%)	13 (1.3%)
Quillivant XR (methylphenidate) (brand or generic formulation)	8 (1.9%)	12 (2.1%)	20 (2.0%)
TOTAL METHYLPHENIDATE	197 (45.8%)	202 (35.1%)	399 (39.7%)
Other (please specify)	9 (2.1%)	1 (0.2%)	10 (1.0%)
Do not know / do not recall	37 (8.6%)	28 (4.9%)	65 (6.5%)

ADHD, Attention Deficit Hyperactivity Disorder; NMU, nonmedical use.

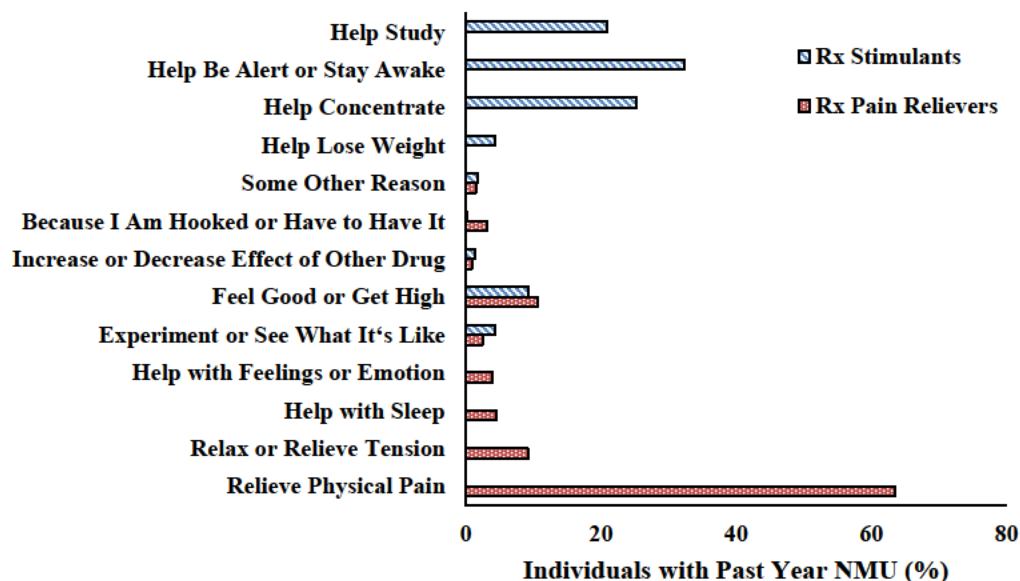
Source: The NOMAD Non-Oral Abuse Survey: Elucidation of Pathways to Non-Oral ADHD Prescription Stimulant Abuse (NOMAD). Results from Table 10. ADHD Stimulants Used In First Non-Oral Abuse.

3.2.3 Reasons/Motivations for NMU

Reasons for NMU of Prescription Stimulants, General Population

Data from the most recently available year of NSDUH (2018) indicated that people aged 12 years or older most commonly reported the reason for their last prescription stimulant NMU event as an attempt to help “be alert or stay awake”, “concentrate”, or “study” (Figure 54). The fourth most common reason reported for NMU of prescription stimulants was an attempt to “feel good or high.” In NSDUH, the frequency of those who reported “feel good or high” as the reason for their last NMU event for prescription stimulants was similar to the frequency of those who reported “feel good or high” as the reason for their last NMU event for prescription pain relievers.

Figure 54. Main reason for last episode of prescription psychotherapeutics NMU, among people with past year NMU aged 12 years or older, National Survey on Drug Use and Health, 2018



NMU, nonmedical use; Rx, prescription.

Note: NMU of prescription use in any way not directed by a doctor, including use without a prescription of one's own; use in greater amounts, more often, or longer than told to take a drug; or use in any other way not directed by a doctor.

Note: Only a subset of reasons apply to each psychostimulant.

Note: Respondents with unknown information for their reason for NMU were excluded from the analysis, including respondents who reported some other reasons but had unknown data in their write-in responses.

Source: FDA-generated figure. Center for Behavioral Health Statistics and Quality. Results from the National Survey on Drug Use and Health, 2018. Retrieved from <https://www.samhsa.gov/data/>.

The main reasons for NMU of prescription stimulants in NSDUH were similar to what has been reported by respondents with a lifetime history of NMU of prescription stimulants included in the Applicant-submitted general population online survey, AR19.MA004. Specifically, AR19.MA004 respondents gave their primary reason for NMU of prescription stimulants as “to enhance performance at work or school”, “for energy”, and “to treat ADHD – regular dose wasn’t working” (Table 21). An additional 14.0% of respondents gave “to get high” as their primary reason for NMU of prescription stimulants, which was less than the 19.8% of respondents that gave “to get high” as their primary reason for NMU of prescription opioid analgesics.

Table 21. Reasons for NMU of prescription opioids and prescription stimulants, among people aged 18 to 49 years, AR19.MA004, an online survey of the general U.S. population conducted by the internet panel company YouGov

Motivation for NMU	Prescription Opioid (N=2,154)				Prescription Stimulant (N=762)			
	Primary reason*		Any reason*		Primary reason*		Any reason*	
	n	%	n	%	n	%	n	%
To treat my pain	1,536	71.3	1,700	78.9				
To treat ADHD – regular dose wasn't working					148	19.4	212	27.8
To enhance performance at work or school					214	28.1	324	42.5
To improve my mood or elevate my spirit					108	14.2	247	32.4
To get high	426	19.8	598	27.8	107	14.0	199	26.1
For energy or stimulation	140	6.5	294	13.7	187	24.5	365	47.9
To enhance effect of other drugs	102	4.7	260	12.1	39	5.1	102	13.4
To prevent or treat withdrawal symptoms					38	5.0	84	11.0
To treat or prevent opioid-related withdrawal	74	3.4	165	7.7				
To treat or prevent withdrawal from alcohol or other drugs (NOT opioid-related)	57	2.7	111	5.2				
By mistake (such as forgot you already took it)	79	3.7	169	7.9	30	3.9	78	10.2
Other reason	77	3.6	164	7.6	38	5.0	54	7.1

ADHD, Attention Deficit Hyperactivity Disorder; NMU, nonmedical use.

Note: * indicates responses are not mutually exclusive and do not necessarily add to 100%. Primary and secondary reasons were asked separately for each medication. A respondent may have endorsed more than one medication hence an opportunity to have reported more than one primary or secondary reasons and combed here.

Source: Nonmedical Use of Prescription Medications among the General Population (AR19.MA004). Results from Table 35. Motivation for NMU of prescription opioids and prescription stimulants.

Reasons for NMU of Prescription Stimulants, Young Adults and Adolescents

The same primary reasons were given by college students with a history of NMU of prescription stimulants included in AR19.MA012 as was reported by respondents of the general population survey AR19.MA004; however, college students, regardless of Greek life participation, reported their primary reason as “to enhance performance at work or school” at a higher frequency than what was reported within the general population sample of AR19.MA004 respondents (39.1% versus 28.1%) (see **Table 22, below and Table 21, above**), with the highest frequency observed among college students who also participated in Greek life (56.0%).

Table 22. Reason for NMU of prescription stimulants, by college enrollment status, AR19.MA012, an online survey of the general U.S. population aged 18 to 26 years conducted by the internet panel company YouGov

PRIMARY Motivation for Prescription Stimulant NMU*	Ages 18 to 26, Prescription Stimulant NMU (N=185)		College Greek (N=25)		College Non-Greek (N=72)		Non-College (N=88)	
	n	%	n	%	n	%	n	%
To enhance performance at work or school	64	34.6	14	56.0	24	33.3	26	29.5
To treat ADD/ADHD	43	23.2	4	16.0	19	26.4	20	22.7
For energy	38	20.5	6	24.0	12	16.7	20	22.7
To improve my mood or elevate my spirit	23	12.4	5	20.0	11	15.3	7	8.0
To get high	21	11.4	2	8.0	9	12.5	10	11.4
To enhance effect of other drugs	11	5.9	4	16.0	4	5.6	3	3.4
To prevent or treat withdrawal symptoms	11	5.9	4	16.0	3	4.2	4	4.5
To control appetite or for weight loss	10	5.4	3	12.0	4	5.6	3	3.4
By mistake (such as forgot you already took it)	8	4.3	1	4.0	2	2.8	5	5.7

ADD, Attention Deficit Disorder; ADHD, Attention Deficit Hyperactivity Disorder; NMU, nonmedical use.

Note: '*' indicates responses are not mutually exclusive and do not necessarily add to 100%. Primary and secondary reasons were asked separately for each medication. A respondent may have endorsed more than one medication hence an opportunity to have reported more than one primary or secondary reasons and combed here.

Note: Greek refers to participation in fraternities or sororities.

Source: Nonmedical Use of Prescription Medications in College Students Involved in Greek Life (AR19.MA012). Results from Table 11. Primary motivation for prescription stimulant NMU, by enrollment in college and Greek life participation.

The patterns of reasons for NMU were somewhat different among 47 youth ages 10 to 17 years reporting lifetime NMU of prescription stimulants from a cross-sectional survey conducted in 2018 in three states (AR19.MA010). A higher proportion of youth than college students from the AR19.MA004 survey said that they used the stimulant to help them study (62%). Other common reasons for NMU in these youth were because their doctor or parent told them to (36%), to stay awake (30%), to get high (40%), and to be cool or fit in (13%) (**Table 23**).

Table 23. Motivation for lifetime* prescription stimulant NMU in a sample of youth ages 10 to 17 from three states (N=47), Study of Non-oral Administration of Prescription Stimulants (SNAPS), AR19.MA010, an anonymous in-person interviewer-facilitated survey of general population youth, conducted by the Substance Abuse Training Center in Public Health at the University of Florida**

Motivation for Use	N	%
To get high	19	40
Out of curiosity	20	43
Because they were pressured to	5	11
To stay awake	14	30
To eat or lose weight	10	21
To help them study	29	62
To relax	21	45
Just because	18	38
Because their doctor or parent told them to	17	36
Because they are safer than "street drugs"	6	13
To be cool or fit in	6	13

NMU, nonmedical use.

Note: '*' excludes respondents with only past 30-day use.

Note: '**' the three states included in the study were California, Texas, and Florida.

Source: FDA-generated table from information in the Study of Non-oral Administration of Prescription Stimulants (SNAPS) report Table 11 (AR19.MA010) Motivation to use by lifetime stimulant pattern.

Reasons NMU of Prescription Stimulants, by API

Table 24 summarizes the primary reasons given by AR19.MA004 respondents for their NMU of prescription stimulants, by route of administration. Briefly, the primary reasons given by respondents that reported lifetime NMU of prescription stimulants by an oral route aligned with the overall patterns of primary use, regardless of route (i.e., enhance performance, energy, treatment of ADHD). However, when respondents reported NMU of prescription stimulants via non-oral routes (i.e., snorting or injecting), the frequency of respondents reporting their primary reason as “to get high” was much greater than what was reported for oral routes. At the same time the frequency of respondents reporting their primary reason as “to treat ADHD – regular dose wasn’t working” was lower for respondents with non-oral NMU of prescription stimulants as compared to respondents with oral NMU of prescription stimulants.

Table 24. Primary reasons for NMU of prescription stimulants, among people aged 18 to 49 years, by route, AR19.MA004, an online survey of the general U.S. population conducted by the internet panel company YouGov

Primary Reason for NMU of Prescription Stimulant	Oral Route* (N=689)		Snorting Route* (N=188)		Injecting Route* (N=27)	
	n	%	n	%	n	%
To treat ADHD – regular dose wasn’t working	143	20.8	20	10.6	2	7.4
To enhance performance at work or school	205	29.8	66	35.1	8	29.6
For energy	170	24.7	64	34.0	6	22.2
To improve my mood or elevate my spirit	101	14.7	31	16.5	7	25.9
To control appetite or for weight loss	48	7.0	15	8.0	7	25.9
To get high	91	13.2	58	30.9	12	44.4
To enhance effect of other drugs	33	4.8	14	7.5	6	22.2
To prevent or treat withdrawal symptoms	31	4.5	8	4.3	6	22.2
By mistake (such as forgot you already took it)	27	3.9	6	3.2	4	14.8
Other reason	27	3.9	8	4.3	2	7.4

ADHD, Attention Deficit Hyperactivity Disorder; NMU, nonmedical use; U.S., United States.

Note: '*' indicates responses are not mutually exclusive and do not necessarily add to 100%. Primary and secondary reasons were asked separately for each medication. A respondent may have endorsed more than one medication hence an opportunity to have reported more than one primary or secondary reasons and combed here.

Source: Nonmedical Use of Prescription Medications among the General Population (AR19.MA004). Results from Table 27. Primary motivation for NMU of prescription stimulants, by route of administration.

3.2.4 Determinants/Risk Factors

Determinants/Risk Factors for NMU of Prescription Stimulants, General Population

Using data collected from respondents of the Applicant-submitted general population cross-sectional survey, AR19.MA004, multivariable logistic regression modelling was used to identify factors that may be associated with lifetime NMU of prescription stimulants (**Table 25**). Briefly, respondents aged 18 to 25 years were more likely to have nonmedically used a prescription stimulant in their lifetime than respondents aged 26 to 49 years (Odds Ratio (OR)=1.44, 95% Confidence Interval (CI): 1.16 to 1.79). A previous diagnosis of ADHD was associated with higher odds of NMU of prescription stimulants (OR=4.42, 95% CI: 3.61 to 5.41), as was a diagnosis of conduct or oppositional defiant disorder (OR=2.17, 95% CI: 1.57 to 3.00), or a psychiatric disorder, such as depression, anxiety, or bipolar disorder (OR=1.60, 95% CI 1.32 to 1.94). Ever use of substances such as marijuana (OR=1.62, 95% CI: 1.31 to 2.01), other illicit drugs (OR=2.84, 95% CI: 2.31 to 3.50), and NMU of prescription opioid analgesics (OR=7.11, 95% CI: 5.95 to 8.51), were all associated with higher odds of NMU of prescription stimulants.

Table 25. Multivariable logistic regression analysis of factors associated with lifetime NMU of prescription stimulants, among people aged 18 to 49 years, AR19.MA004, an online survey of the general U.S. population conducted by the internet panel company YouGov

Variable	Prescription stimulant NMU in lifetime (N=762)		Unadjusted OR		Adjusted OR	
	n/total ^a	%	OR	95% CI	OR	95% CI
Age						
18 to 25	155/2668	5.8	0.89	0.74-1.06	1.44	1.16-1.79
26 to 49	607/9332	6.5	Ref			
Sex						
Female	338/6131	5.5	0.75	0.65-0.87	0.81	0.68-0.96
Male	424/5869	7.2	Ref			
Race/ethnicity						
White	522/7243	7.2	1.46	1.25-1.71	1.07	0.89-1.29
Non-White	240/4757	5.1	Ref			
Lifetime diagnosis of ADHD						
Yes	293/1207	24.3	7.06	6.01-8.29	4.42	3.61-5.41
No	469/10793	4.4	Ref			
Lifetime diagnosis of psychiatric disorder (depression, anxiety, or bipolar disorder)						
Yes	552/5131	10.8	3.82	3.25-4.50	1.60	1.32-1.94
No	210/6869	3.1	Ref			
Lifetime diagnosis of alcohol or substance use disorder						
Yes	227/851	26.7	7.22	6.06-8.60	1.24	0.97-1.57
No	535/11149	4.8	Ref			
Lifetime diagnosis of conduct or oppositional defiant disorder						
Yes	127/371	34.2	9.01	7.17-11.33	2.17	1.57-3.00
No	635/11629	5.5	Ref			
Binge alcohol use, past 30 days						
Yes	61/537	11.4	1.97	1.49-2.60	0.94	0.68-1.30
No	701/11463	6.1	Ref			
Marijuana use in lifetime						
Yes	560/5157	10.9	4.00	3.39-4.72	1.62	1.31-2.01
No	202/6843	3.0	Ref			
Other illicit drug (cocaine, heroin, or illicit stimulant) use in lifetime						
Yes	383/1676	22.9	7.77	6.67-9.06	2.84	2.31-3.50
No	379/10324	3.7	Ref			
Nonmedical use of prescription opioids in lifetime						
Yes	503/2154	23.4	11.28	9.62-13.22	7.11	5.95-8.51
No	259/9846	2.6	Ref			

ADHD, Attention Deficit Hyperactivity Disorder; CI, confidence interval; NMU, nonmedical use; OR, odds ratio; Ref, reference; U.S., United States.

Note: ^a* The numerator represents the total number with lifetime NMU of prescription stimulants for a particular row; the denominator represents the total number having a specific characteristic within a row; and the proportion represents the percentage with lifetime NMU of prescription stimulants within a specific row. For example, among 2,668 individuals aged 18-25 years, 5.8% had lifetime NMU of prescription stimulants. The total sample size for the analysis was 12,000, including 762 with lifetime NMU of prescription stimulants and 11,238 without lifetime NMU of prescription stimulants (reference category).

Note: The full multivariable models included age, sex, race/ethnicity, lifetime diagnosis of ADHD, lifetime diagnosis of psychiatric disorder (depression, anxiety, or bipolar disorder), lifetime diagnosis of conduct or oppositional defiant disorder, binge alcohol use in the past 30 days, lifetime use of marijuana, other illicit drug use (cocaine, heroin, or illicit stimulant use) in lifetime, and lifetime NMU of prescription opioids.

Source: Nonmedical Use of Prescription Medications among the General Population (AR19.MA004). Results from Table 50. Factors associated with lifetime NMU of prescription stimulants (N=12,000).

Determinants/Risk Factors for NMU of Prescription Stimulants via a Non-oral Route, General Population

Among AR19.MA004 respondents with a lifetime history of NMU of prescription stimulants, multivariable logistic regression modelling was also used to identify factors that were associated with lifetime NMU of prescription stimulants via a non-oral route compared to an oral route only (**Table 26**). Briefly, respondents between the ages of 18 and 25 years were more likely to nonmedically use a prescription stimulant, via a non-oral route versus an oral route, when compared to those respondents aged 26 to 49 years (OR=1.60, 95% CI: 1.01 to 2.53). Other factors that were associated with increased odds of NMU of prescription stimulants, via non-oral routes compared to oral routes, were race/ethnicity (white vs. non-white; OR=2.05, 95% CI: 1.36 to 3.10), lifetime diagnosis of a psychiatric disorder

(OR=1.22, 95% CI: 0.78 to 1.89), alcohol or substance use disorder (OR=1.73, 95% CI: 1.13 to 2.64), or conduct or oppositional defiant disorder (OR=2.60, 95% CI: 1.52 to 4.45). History of substance use, such as binge alcohol use in the past 30 days (OR=1.83, 95% CI: 1.02 to 3.30), lifetime use of other illicit drugs (OR=3.90, 95% CI: 2.40 to 6.35), and lifetime NMU of prescription opioid analgesics (OR=1.80, 95% CI: 1.17 to 2.79) were all associated with higher odds of NMU of prescription stimulants, via a non-oral route compared to an oral route. A previous diagnosis of ADHD was associated with reduced odds of NMU of a prescription stimulant, via a non-oral route compared to an oral route (OR=0.56, 95% CI 0.37 to 0.84).

Table 26. Multivariable logistic regression analysis of factors associated with lifetime NMU of prescription stimulants via a non-oral route compared to only oral route, among people aged 18 to 49 years, AR19.MA004, an online survey of the general U.S. population conducted by the internet panel company YouGov

Variable	Prescription stimulant NMU via non-oral routes in lifetime (N=208)		Unadjusted OR		Adjusted OR	
	n/total*	%	OR	95% CI	OR	95% CI
Age						
18 to 25	42/150	28.0	1.02	0.69-1.52	1.60	1.01-2.53
26 to 49	166/602	27.6	Ref		Ref	
Sex						
Female	89/330	27.0	0.94	0.68-1.30	0.99	0.69-1.43
Male	119/422	28.2	Ref		Ref	
Race/ethnicity						
White	159/516	30.8	1.70	1.18-2.45	2.05	1.36-3.10
Non-White	49/236	20.8	Ref		Ref	
Lifetime diagnosis of ADHD						
Yes	78/290	26.9	0.94	0.68-1.31	0.56	0.37-0.84
No	130/462	28.1	Ref		Ref	
Lifetime diagnosis of psychiatric disorder (depression, anxiety, or bipolar disorder)						
Yes	164/543	30.2	1.62	1.11-2.37	1.22	0.78-1.89
No	44/209	21.1	Ref		Ref	
Lifetime diagnosis of alcohol or substance use disorder						
Yes	98/223	44.0	2.99	2.13-4.19	1.73	1.13-2.64
No	110/529	20.8	Ref		Ref	
Lifetime diagnosis of conduct or oppositional defiant disorder						
Yes	57/125	45.6	2.64	1.78-3.93	2.60	1.52-4.45
No	151/627	24.1	Ref		Ref	
Binge alcohol use, past 30 days						
Yes	25/60	41.7	1.99	1.16-3.41	1.83	1.02-3.30
No	183/692	26.5	Ref		Ref	
Marijuana use in lifetime						
Yes	167/555	30.1	1.64	1.11-2.42	0.61	0.35-1.06
No	41/197	20.8	Ref		Ref	
Other illicit drug (cocaine, heroin, or illicit stimulant) use in lifetime						
Yes	152/380	40.0	3.76	2.65-5.34	3.90	2.40-6.35
No	56/372	15.1	Ref		Ref	
Nonmedical use of prescription opioids in lifetime						
Yes	169/496	34.1	2.88	1.95-4.24	1.80	1.17-2.79
No	39/256	15.2	Ref		Ref	

ADHD, Attention Deficit Hyperactivity Disorder; CI, confidence interval; NMU, nonmedical use; OR, odds ratio, Ref, reference; U.S., United States.

Note: * The numerator represents the total number who reported lifetime NMU of prescription stimulants via non-oral routes for a particular row; the denominator represents the total number having a specific characteristic within a row; and the proportion represents the percentage with lifetime NMU of prescription stimulants via non-oral routes within a specific row. For examples, among 150 individuals ages 18-25 years, 28.0% reported lifetime NMU of prescription stimulants via non-oral routes. The total sample size for the analysis was 752, including 208 with lifetime NMU of prescription stimulants via non-oral routes and 544 with lifetime NMU of prescription stimulants via oral routes only (reference category).

Note: The full multivariable models included age, sex, race/ethnicity, lifetime diagnosis of ADHD, lifetime diagnosis of psychiatric disorder (depression, anxiety, or bipolar disorder), lifetime diagnosis of conduct or oppositional defiant disorder, binge alcohol use in the past 30 days, lifetime use of marijuana, other illicit drug use (cocaine, heroin, or illicit stimulant use) in lifetime, and lifetime NMU of prescription opioids.

Source: Nonmedical Use of Prescription Medications among the General Population (AR19.MA004). Results from Table 10. Factors associated with lifetime NMU of prescription stimulants via *non-oral routes* compared with oral routes only (N=752).

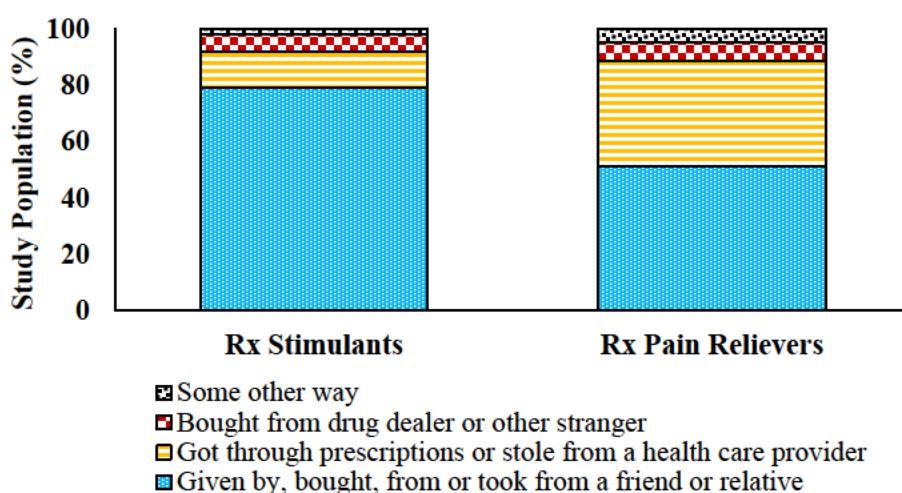
3.2.5 Source of Prescription Stimulants

Source of Prescription Stimulants for NMU, General Population

Data from the most recent available year of NSDUH (2018) estimated 79.1% of people aged 12 years or older identified the source of their last nonmedically used prescription stimulant as “given by, bought from, or took from a friend or relative,” followed by an estimated 12.8% citing their source as “got through prescription(s) or stole from health care provider” (Figure 55). For comparison, an estimated 51.3% of people identified the source of their last nonmedically used prescription pain reliever as “given by, bought from, or took from a friend or relative,” followed by 37.6% citing their source as “got through prescriptions(s) or stole from health care provider.”

Respondents with NMU of prescription stimulants in their lifetime enrolled in the Applicant-submitted general population online survey, AR19.MA004, reported a similar primary source of prescription stimulants as observed in NSDUH, with 63.7% of respondents reporting the source of their prescription stimulant as a “bought/given/stole it from family or friend” (Table 27). When AR19.MA004 respondents were allowed to select more than one option as their primary source for NMU a larger proportion, 41.7%, reported the source of their prescription stimulant as, “my own prescription from one doctor or several doctors,” than in NSDUH. AR19.MA004 respondents reported the same primary sources for NMU of prescription stimulants and prescription opioid analgesics; however, a greater proportion of respondents with NMU of prescription stimulants reported “bought/given/stole it from family or friend” as their source when compared to respondents with NMU of prescription opioid analgesics, while a lower proportion of respondents with NMU of prescription stimulants reported “my own prescription from one doctor or several doctors” as their source when compared to respondents with NMU of prescription opioid analgesics.

Figure 55. Source of prescription stimulants and pain relievers for most recent NMU event, among people aged 12 years or older, National Survey on Drug Use and Health, 2018



NMU, nonmedical use; Rx, prescription.

Note: Misuse (i.e., NMU) of prescription use in any way not directed by a doctor, including use without a prescription of one's own; use in greater amounts, more often, or longer than told to take a drug; or use in any other way not directed by a doctor.

Note: Respondents were asked to choose only one source. Respondents with unknown data on source for most recent misuse and respondents with unknown or invalid responses to the corresponding other-specify questions were excluded from the analysis.

Note: Some Other Way includes write-in responses not already listed in this table or responses with insufficient information that could allow them to be placed in another category.

Source: FDA-generated figure. Center for Behavioral Health Statistics and Quality. Results from the National Survey on Drug Use and Health, 2018. Retrieved from <https://www.samhsa.gov/data/>.

Table 27. Source of prescription opioids and prescription stimulants for NMU, among people aged 18 to 49 years, AR19.MA004, an online survey of the general U.S. population conducted by the internet panel company YouGov

Source of Procurement	Prescription Opioid* (N=2,154)		Prescription Stimulant* (N=762)	
	n	%	n	%
Bought/given/stole it from family or friend	957	44.4	485	63.7
My own prescription from one doctor or several doctors	1,456	67.6	318	41.7
Bought it from a dealer (a known seller)	178	8.3	76	10.0
Bought it online without a doctor's visit	91	4.2	66	8.7
Traded for it	56	2.6	31	4.1
Wrote or bought a fake prescription	30	1.4	19	2.5
Stole them (from someone I did not know)	34	1.6	11	1.4
Other source	38	1.8	14	1.8

NMU, nonmedical use; U.S., United States.

Note: '*' indicates responses are not mutually exclusive and do not necessarily add to 100%.

Source: Nonmedical Use of Prescription Medications among the General Population (AR19.MA004). Results from Table 37. Source of procurement of prescription opioids and prescription stimulants used for NMU.

Source of Prescription Stimulants for NMU, Young Adults and Adolescents

Among college students included in AR19.MA012, the source of prescription stimulants was very similar to what was observed in the general population sample of AR19.MA004 respondents. College students in AR19.MA012 reported the most common sources of prescription stimulants as “bought/given/stole it from a family or friend” or “my own prescription from one doctor or several doctors.” Individuals enrolled in college that also participated in Greek life reported “my own prescription from one doctor or several doctors” as the procurement source at a higher frequency than those college students not participating in Greek life (52.0% vs. 34.3%) (Table 28).

Table 28. Source of prescription stimulants for NMU, by Greek life participation, AR19.MA012, an online survey of the general U.S. population aged 18 to 26 years conducted by the internet panel company YouGov

Source of Procurement*	Study Population (N=583)		Greek (N=175)		Non-Greek (N=408)	
	n	%	n	%	n	%
Bought/given/stole it from family or friend	386	66.2	112	64.0	274	67.2
My own prescription from one doctor or several doctors	231	39.6	91	52.0	140	34.3
Bought it from a dealer (a known seller)	77	13.2	27	15.4	50	12.3
Bought it online without a doctor's visit	65	11.1	34	19.4	31	7.6
Traded for it	31	5.3	9	5.1	22	5.4
Wrote or bought a fake prescription	21	3.6	11	6.3	10	2.5
Stole them (from someone I did not know)	16	2.7	9	5.1	7	1.7

NMU, nonmedical use; U.S., United States.

Note: Greek refers to participation in fraternities or sororities.

Note: '*' indicates responses are not mutually exclusive and do not necessarily add to 100%.

Source: Nonmedical Use of Prescription Medications in College Students Involved in Greek Life (AR19.MA012). Results from Table 39. Source of procurement of prescription stimulants used for NMU by participation in Greek life.

Similar to NSDUH, AR19.MA004, and AR19.MA012, youth ages 10 to 17 years who reported receiving diverted prescription stimulant medications (AR19.MA010) reported common sources of diverted medication as being given a prescription stimulant for free (71%) as well as buying (35%), borrowing

(43%), and stealing (25%) from someone (**Table 29**). Respondents who reported non-oral use *and* receiving diverted prescription stimulants reported each of the diversion methods more frequently than those who reported only oral use *and* receiving diverted prescription stimulants. Of the youth who reported requests for diversion or actual diversion of their own prescription stimulants, common methods included being asked to give a prescription stimulant to someone (75%), selling their prescription stimulant (44%), and giving their prescription stimulant to someone for free (44%).

Table 29. Incoming and outgoing diversion of prescription stimulants in youth ages 10 to 17 years, by route of administration, AR19.MA010, an anonymous in-person interviewer-facilitated survey of general population youth, conducted by the Substance Abuse Training Center in Public Health at the University of Florida

Source	Oral Only Use of Prescription Stimulants	Any Report of Non-Oral Use of Prescription Stimulants	Any Route of Use of Prescription Stimulants
Incoming Diversion		N (%) Reporting Diversion Source out of Respondents Reporting Receiving Diverted Prescription Stimulant Medication	
Total N Reporting Incoming Diversion	37	14	51
Stole Prescription Stimulant(s)	7 (19)	6 (43)	13 (25)
Given Prescription Stimulant(s) for Free	25 (68)	11 (79)	36 (71)
Borrowed Prescription Stimulant(s)	15 (41)	7 (50)	22 (43)
Bought Prescription Stimulant(s) from Someone	11 (30)	7 (50)	18 (35)
Outgoing Diversion		N (%) Reporting Diversion Source out of Respondents Reporting Diversion of Their Prescription Stimulant Medication	
Total N Reporting Outgoing Diversion	50	18	68
Asked to Sell Prescription Stimulant(s)	20 (40)	10 (56)	30 (44)
Asked to Give Prescription Stimulant(s) to Someone	38 (76)	13 (72)	51 (75)
Asked to Trade Prescription Stimulant(s)	15 (30)	8 (44)	23 (34)
Sold Prescription Stimulant(s)	12 (24)	11 (61)	23 (34)
Gave Prescription Stimulant(s) for Free	19 (38)	11 (61)	30 (44)
Traded Prescription Stimulant(s)	8 (16)	6 (33)	14 (21)
Got Prescription Stimulant(s) Stolen	6 (12)	2 (11)	8 (12)

Source: FDA-generated table from information in the Study of Non-oral Administration of Prescription Stimulants (SNAPS) (AR19.MA010, table 12). Diversion rates among stimulant non-users, oral only users, and non-oral users.

Source of Prescription Stimulants for NMU, by Route of Administration

Among respondents with lifetime NMU of a prescription stimulant via a non-oral route of administration (i.e., snorting or injecting) included in the Applicant-submitted online survey, AR19.MA004, 82.3% of respondents reported their source of procurement for a prescription stimulant as “bought/given/stole it from a family or friend,” while 63.0% of respondents with lifetime NMU of a prescription stimulant, via an oral route of administration, reported their source as “bought/given/stole it from a family or friend.” The source of procurement, “my own prescription from one doctor or several doctors,” was given by 43.4% of respondents with lifetime NMU of a prescription stimulant via an oral route of administration and 34.4% of respondents with lifetime NMU of a prescription stimulant via a non-oral route of administration (**Table 30**).

Table 30. Source of prescription stimulants for NMU, among people aged 18 to 49 years, by route of administration, AR19.MA004, an online survey of the general U.S. population conducted by the internet panel company YouGov

Source of Procurement	Oral Route Route* (N=689)		Snorting Route* (N=188)		Injecting Route* (N=27)	
	n	%	n	%	n	%
Bought/given/stole it from family or friend	434	63.0	153	81.4	24	88.9
My own prescription from one doctor or several doctors	299	43.4	60	31.9	14	51.9
Bought it from a dealer (a known seller)	67	9.7	45	23.9	12	44.4
Bought it online without a doctor's visit	60	8.7	25	13.3	10	37.0
Traded for it	28	4.1	15	8.0	2	7.4
Wrote or bought a fake prescription	17	2.5	10	5.3	5	18.5
Stole them (from someone I did not know)	8	1.2	8	4.3	3	11.1
Other source	10	1.5	1	0.5	-	-

NMU, nonmedical use; U.S. United States.

Note: '*' indicates responses are not mutually exclusive and do not necessarily add to 100%.

Source: Nonmedical Use of Prescription Medications among the General Population (AR19.MA004). Results from Table 30. Source of procurement of prescription stimulants used for NMU, by route of administration.

Source of Prescription Stimulants for NMU among Enriched Populations

As part of AR19.MA003, U.S. adults and adolescents with NMU of prescription stimulants in the past 30 days seeking treatment or being assessed for SUD provided information on the procurement sources of prescription stimulants (**Table 31** and **Table 32**). Among adult ASI-MV respondents, the most common sources reported for NMU in the past 30 days for any prescription stimulant were “family/friend” (55.3%), “dealer” (26.6%), and their “own prescription” (22.8%). These sources were similar for both prescription amphetamines and methylphenidates. Among adolescent CHAT® respondents, a similar pattern of stimulant procurement sources was reported including “family/friend” (54.6%), “dealer” (27.5%), and their “own prescription” (17.8%). Adolescent CHAT® respondents also reported similar patterns of procurement sources for both prescription amphetamines and methylphenidates.

Table 31. Source of prescription stimulants, among ASI-MV® respondents aged 18 years or older with nonmedical prescription stimulant use in the past 30 days, AR19.MA003 Study

Categories, Prescription Stimulants	Number of past 30-day NMU cases		Family/friend		Dealer		Own prescription		Stolen		Multiple doctors		Rx Forgery		Internet		Other	
	n	n	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Any stimulant	8,958	4,952	55.28	2,386	26.64	2,040	22.77	291	3.25	168	1.88	39	0.44	40	0.45	1,614	18.02	
Any amphetamine	7,269	4,071	56.00	1,855	25.52	1,433	19.71	197	2.71	125	1.72	22	0.30	20	0.28	1,125	15.48	
Amphetamine ER	3,756	2,119	56.42	1,076	28.65	545	14.51	116	3.09	56	1.49	17	0.45	12	0.32	548	14.59	
Amphetamine IR	4,527	2,567	56.70	1,186	26.20	826	18.25	104	2.30	78	1.72	6	0.13	10	0.22	677	14.95	
Amphetamine salt	6,712	3,766	56.11	1,762	26.25	1,183	17.63	160	2.38	102	1.52	11	0.16	14	0.21	1,018	15.17	
Dextroamphetamine	261	104	39.85	58	22.22	44	16.86	16	6.13	14	5.36	7	2.68	5	1.92	70	26.82	
Lisdexamfetamine	1,186	605	51.01	269	22.68	220	18.55	47	3.96	18	1.52	10	0.84	6	0.51	165	13.91	
Any methylphenidate*	3,112	1,587	51.00	815	26.19	560	17.99	129	4.15	63	2.02	20	0.64	19	0.61	641	20.60	
Methylphenidate ER	1,620	822	50.74	419	25.86	188	11.60	89	5.49	31	1.91	10	0.62	8	0.49	349	21.54	
Methylphenidate IR	1,363	697	51.14	415	30.45	191	14.01	51	3.74	23	1.69	7	0.51	7	0.51	238	17.46	
Dxmethylphenidate	383	188	49.09	92	24.02	41	10.70	19	4.96	11	2.87	2	0.52	4	1.04	76	19.84	
Methylphenidate	2,942	1,487	50.54	779	26.48	520	17.68	119	4.04	54	1.84	19	0.65	15	0.51	599	20.36	

ASI-MV®: Addiction Severity Index Multimedia Version; ER, extended release; IR, immediate release; NMI, nonmedical use.

Note: Percentages calculated for small sample sizes ($n < 30$ cases) are unstable and should be interpreted with caution.

Note: Categories are not mutually exclusive and therefore do not sum to 100%.

Note: *Y includes both methylphenidate and dxmethylphenidate stimulant categories.

Source: Analysis of Prescription Stimulants in ASI-MV® and CHAT® (AR19.MA003). Results from Table 10. Procurement sources of prescription stimulants among those reporting past 30-day NMU of prescription stimulants in the ASI-MV® network (01/01/2010 – 9/30/2017).

Table 32. Source of prescription stimulants, among CHAT® respondents aged 18 years or younger with nonmedical prescription stimulant use in the past 30 days, AR19.MA003 Study

Categories, Prescription Stimulants	Number of past 30-day NMU cases		Family/friend		Dealer		Own prescription		Stolen		Multiple doctors		Rx Forgery		Internet		Other	
	n	n	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Any stimulant	870	475	54.60	239	27.47	155	17.82	77	8.85	7	0.80	4	0.46	3	0.34	208	23.91	
Any amphetamine	735	397	54.01	189	25.71	105	14.29	55	7.48	4	0.54	3	0.41	2	0.27	161	21.90	
Amphetamine ER	537	275	51.21	128	23.84	96	17.88	28	5.21	4	0.74	1	0.19	1	0.19	99	18.44	
Amphetamine IR	331	179	54.08	95	28.70	20	6.04	31	9.37	0	0.00	1	0.30	2	0.60	75	22.66	
Amphetamine salt	632	336	53.16	169	26.74	60	9.49	45	7.12	2	0.32	2	0.32	2	0.32	137	21.68	
Dextroamphetamine	20	6	30.00	0	0.00	3	15.00	4	20.0	0	1	5.00	0	0.00	1	5.00	4	20.00
Lisdexamfetamine	236	112	47.46	39	16.53	53	22.46	11	4.66	1	0.42	1	0.42	1	0.42	40	16.95	
Any methylphenidate*	362	188	51.93	86	23.76	63	17.40	31	8.56	2	0.55	2	0.55	2	0.55	68	18.78	
Methylphenidate ER	240	129	53.75	56	23.33	39	16.25	14	5.83	2	0.83	2	0.83	1	0.42	44	18.33	
Methylphenidate IR	116	62	53.45	32	27.59	4	3.45	12	10.3	4	0	0.00	1	0.86	0	0.00	26	22.41
Dxmethylphenidate	68	24	35.29	13	19.12	20	29.41	6	8.82	0	0.00	0	0.00	1	1.47	10	14.71	
Methylphenidate	325	171	52.62	77	23.69	49	15.08	25	7.69	2	0.62	2	0.62	1	0.31	62	19.08	

CHAT®: Comprehensive Health Assessment for Teens; ER, extended release; IR, immediate release; NMU, nonmedical use.

Note: Percentages calculated for small sample sizes ($n < 30$ cases) are unstable and should be interpreted with caution.

Note: Categories are not mutually exclusive and therefore do not sum to 100%.

Note: *Y includes both methylphenidate and dxmethylphenidate stimulant categories.

Source: Analysis of Prescription Stimulants in ASI-MV® and CHAT® (AR19.MA003). Results from Table 24. Procurement sources of prescription stimulants among those reporting past 30-day NMU of prescription stimulants in the CHAT® network (01/01/2010 – 09/30/2017).

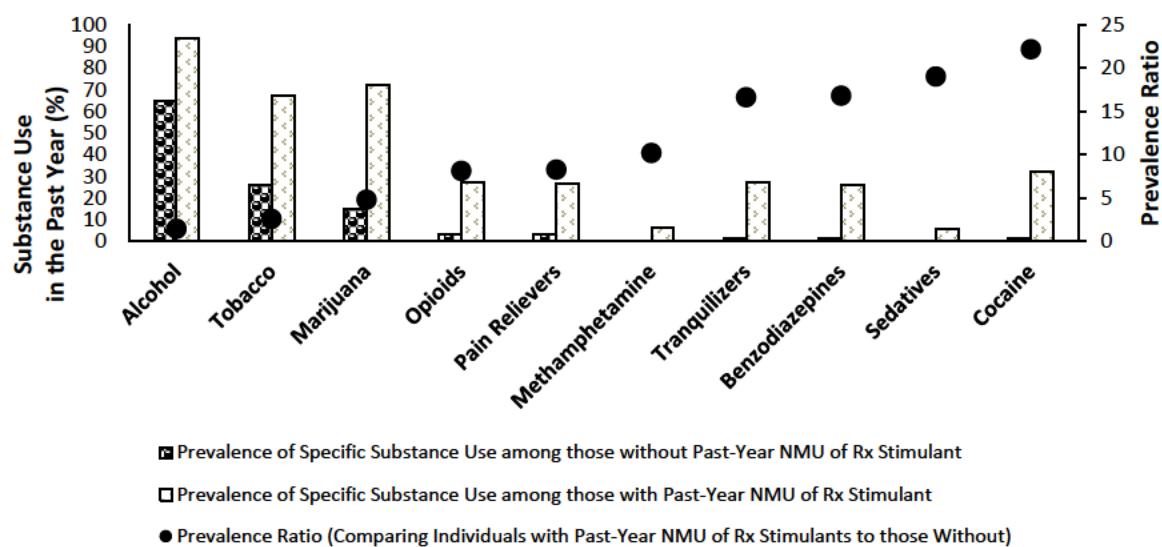
3.2.6 Polysubstance Use and NMU of Prescription Stimulants

3.2.6.1 General U.S. Population Studies

Overall NMU of Prescription Stimulants

Polysubstance use is common among people reporting NMU of prescription stimulants. 2018 NSDUH data showed that within the general U.S. population the most common additional substances used by people aged 12 years and older who reported past year prescription stimulant NMU were alcohol (94.1%), marijuana (72.1%) and tobacco (67.5%) (**Figure 56**). Although at a lower prevalence, alcohol, marijuana, and tobacco were also the most commonly reported substances used among those without stimulant NMU in the past year. When comparing people with prescription stimulant NMU to those without prescription stimulant NMU, the polysubstance prevalence ratio was highest for cocaine (22.2) and sedatives (19.0) among the selected substances in **Figure 56**.

Figure 56. NMU of prescription stimulants and polysubstance use, among people aged 12 years or older, National Survey on Drug Use and Health, 2018



NMU, nonmedical use; Rx, prescription.

Note: NMU (i.e., misuse) of prescription use in any way not directed by a doctor, including use without a prescription of one's own; use in greater amounts, more often, or longer than told to take a drug; or use in any other way not directed by a doctor.

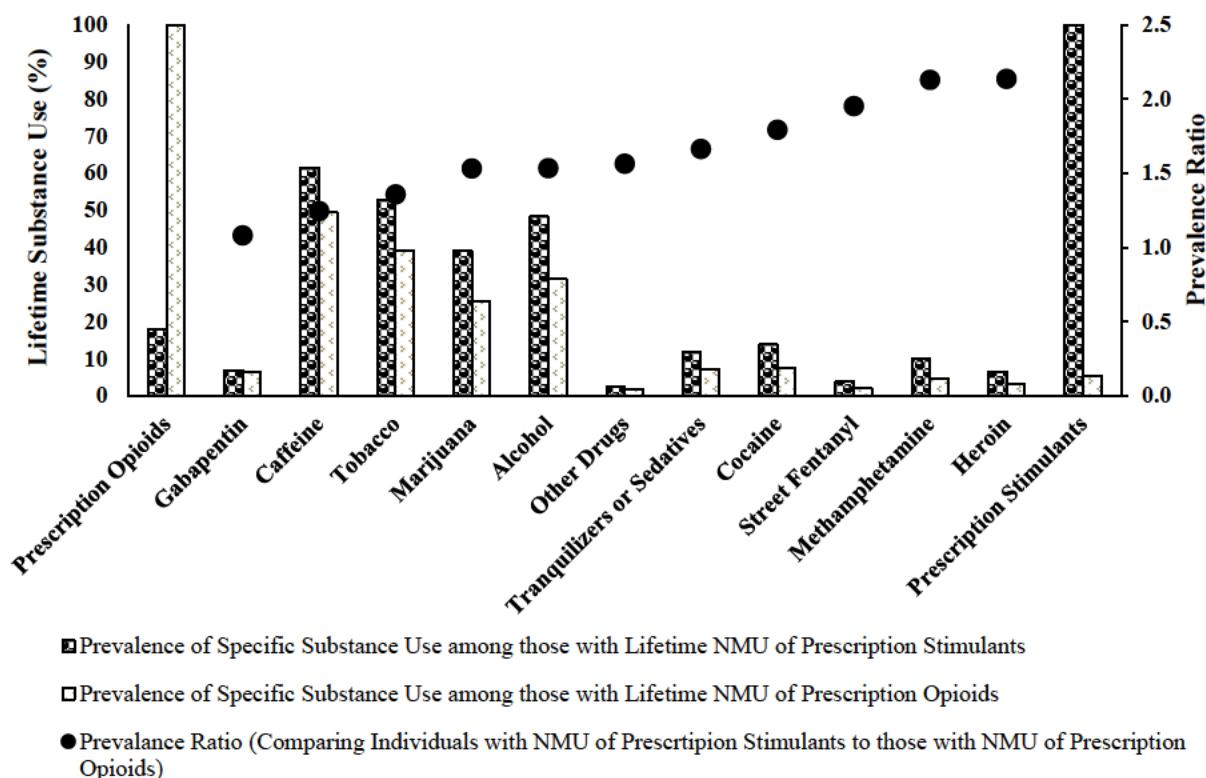
Note: Prevalence ratios for each substance were calculated by taking proportion of people with NMU of that substance who also had prescription stimulant NMU in the past year over the proportion of people with NMU of that substance who did nonmedically use prescription stimulants in the past year. People without NMU of prescription stimulants may or may not have reported NMU of other prescription medications in the past year. For example, the prevalence of cocaine use in the past year among people who also nonmedically used prescription stimulants in the past year was 32.17%, while the prevalence of cocaine use in the past year among people without NMU of prescription stimulants in the past year was 1.45%. The prevalence ratio for cocaine was calculated by taking the proportion of those two values (i.e., 32.17% divided by 1.45%), which resulted in a prevalence ratio of 22.2 for cocaine.

Source: FDA-generated figure. Center for Behavioral Health Statistics and Quality. Results from the National Survey on Drug Use and Health, 2018. Retrieved using the crosstab analyses tool made available by the Public-use Data Analysis System provided by SAMHSA <https://www.samhsa.gov/data/>

Polysubstance use patterns were also compared between people that reported lifetime NMU of prescription stimulants to people that reported lifetime NMU of prescription opioid analgesics, within the Applicant-submitted survey data from AR19.MA004 (**Figure 57**). In general, people with lifetime NMU of prescription stimulants reported use of nearly all drugs assessed more frequently than respondents with lifetime NMU of prescription opioid analgesics. The most frequently reported substances by both groups were caffeine, tobacco, alcohol, and marijuana. Compared to people who ever nonmedically used a prescription opioid analgesic, individuals who ever nonmedically used a prescription stimulant were more

likely to also report use of other substances, especially heroin, methamphetamine, and street fentanyl, indicated by prevalence ratios greater than 2.0.

Figure 57. Polysubstance use, among people aged 18 to 49 years with lifetime NMU of prescription stimulants or opioid analgesics, AR19.MA004, an online survey of the general U.S. population conducted by the internet panel company YouGov



NMU, nonmedical use; U.S., United States.

Note: Responses are not mutually exclusive and do not necessarily add to 100%.

Note: Other drugs include acid, antidepressants, kratom, MDMA, molly, psychedelic drugs, Subutex, and Xanax.

Note: Prevalence ratios for each substance were calculated by taking proportion of people with lifetime NMU of that substance who also had lifetime NMU of prescription stimulant over the proportion of people with lifetime NMU of that substance who also had lifetime NMU of prescription opioids.

Note: Prevalence ratios were not calculated for prescription stimulants or prescription opioids.

Source: FDA-generated figure. Nonmedical Use of Prescription Medications among the General Population (AR19.MA004). Results from Table 13. Other drugs used at the same time as prescription stimulants for NMU and Table 36. Other drugs used at the same time as prescription opioids and prescription stimulants for NMU.

NMU of Prescription Stimulants among Young Adults

Table 33 summarizes polysubstance use among respondents between the ages of 18 and 26 years with a history of NMU of prescription stimulants included in AR19.MA012. Overall, cocaine (87.6%) was the most frequently reported other substance used, followed by caffeine (52.4%), alcohol (43.8%), tobacco (42.2%), and marijuana (42.2%). Respondents enrolled in college (i.e., Greek and Non-Greek participants combined) were over 1.5 times as likely to report additional use of street fentanyl, tranquilizers or sedatives, heroin, and gabapentin as compared to those not enrolled in college, while respondents not enrolled in college were over 1.5 times as likely to report additional use of prescription opioid analgesics and marijuana as compared to those enrolled in college.

Table 33. NMU of prescription stimulants and polysubstance use, by college enrollment status, AR19.MA012, an online survey of the general U.S. population aged 18 to 26 years conducted by the internet panel company YouGov

Other Drugs Used Concomitantly*	Ages 18 to 26, Prescription Stimulant NMU (N=185)		College Greek (N=25)		College Non-Greek (N=72)		Non-College (N=88)	
	n	%	n	%	n	%	n	%
Cocaine	162	87.6	19	76.0	68	94.4	75	85.2
Caffeine	97	52.4	11	44.0	35	48.6	51	58.0
Alcohol	81	43.8	13	52.0	22	30.6	46	52.3
Tobacco	78	42.2	11	44.0	29	40.3	38	43.2
Marijuana	78	42.2	11	44.0	21	29.2	46	52.3
Prescription opioids	20	10.8	2	8.0	5	6.9	13	14.8
Tranquilizers or sedatives (for example valium, benzodiazepines)	18	9.7	5	20.0	7	9.7	6	6.8
Methamphetamine	12	6.5	4	16.0	3	4.2	5	5.7
Heroin	11	5.9	3	12.0	4	5.6	4	4.5
Gabapentin	8	4.3	1	4.0	4	5.6	3	3.4
Street fentanyl	6	3.2	3	12.0	2	2.8	1	1.1

NMU, nonmedical use; U.S., United States.

Note: Greek refers to participation in fraternities or sororities.

Note: ** indicates responses are not mutually exclusive and do not necessarily add to 100%.

Source: Nonmedical Use of Prescription Medications in College Students Involved in Greek Life (AR19.MA012). Results from Table 13. Other drugs used at the same time as prescription stimulants for NMU, by enrollment in college and Greek life participation.

Polysubstance Use and NMU of Prescription Stimulants, by Route of Administration

Table 34 summarizes polysubstance use among respondents of AR19.MA004 with NMU of prescription stimulants, by route of administration. For all routes, AR19.MA004 respondents with NMU of prescription stimulants most frequently reported also using caffeine, alcohol, tobacco, and marijuana. For most drugs assessed, respondents with NMU of prescription stimulants via a non-oral route (i.e., snorting, injecting) reported higher polysubstance use than those reporting NMU via an oral route. Respondents reporting NMU of prescription stimulants via snorting were at least two times as likely to also report use of cocaine, heroin, street fentanyl, and methamphetamine, when compared to respondents with NMU of prescription stimulants via an oral route. Respondents reporting NMU of prescription stimulants via injecting were at least two times as likely to also report use of heroin, street fentanyl, methamphetamine, tranquilizers or sedatives, or other drugs, when compared to respondents with NMU of prescription stimulants via an oral route. Respondents reporting NMU of prescription stimulants via injecting were 2.5 times as likely to also report use of street fentanyl, when compared to respondents with NMU of prescription stimulants via snorting.

Table 34. Polysubstance use, among people aged 18 to 49 years with lifetime NMU of prescription stimulants, by route of nonmedical prescription stimulant use, AR19.MA004, an online survey of the general U.S. population conducted by the internet panel company YouGov

Other Drugs Used Concomitantly	Oral Route* (N=689)		Snorting Route* (N=188)		Injecting Route* (N=27)	
	n	%	n	%	n	%
Tobacco	354	51.4	139	73.9	17	63.0
Caffeine	435	63.1	121	64.4	13	48.2
Alcohol	333	48.3	121	64.4	10	37.0
Marijuana	263	38.2	113	60.1	10	37.0
Cocaine	88	12.8	53	28.2	5	18.5
Heroin	43	6.2	28	14.9	5	18.5
Street fentanyl	26	3.8	14	7.5	5	18.5
Methamphetamine	69	10.0	42	22.3	6	22.2
Prescription opioids	120	17.4	55	29.3	7	25.9
Tranquilizers or sedatives	82	11.9	40	21.3	8	29.6
Gabapentin	42	6.1	19	10.1	3	11.1
Other drugs	17	2.5	8	4.3	2	7.4

NMU, nonmedical use; U.S., United States.

Note: * indicates response options are not mutually exclusive as respondents could endorse multiple concomitant drugs.

Note: Other drugs include acid, antidepressants, kratom, MDMA, molly, psychedelic drugs, Subutex, and Xanax.

Source: Nonmedical Use of Prescription Medications among the General Population (AR19.MA004). Results from Table 29. Other drugs used at the same time as prescription stimulants for NMU, by route of administration.

3.2.6.2 People Seeking Advice or Healthcare

Data from NPDS were analyzed for polysubstance use among cases with NMU of prescription and illicit stimulants. From 2001 through 2018, 36.5% of NPDS exposure cases involving NMU of CII prescription stimulants also involved additional substances, including alcohol (23.4%), benzodiazepines (19.2%), prescription or illicit opioids (16.9%), cannabis (9.0%), cocaine or methamphetamine (6.8%), or muscle relaxants (2.8%) (**Table 35**). In comparison, 45.3% of NPDS exposure cases involving NMU of illicit stimulants and 51.6% of NPDS exposure cases involving NMU of unknown amphetamines also involved additional substances. Use of prescription or illicit opioids or cannabis differed greatly between multi-substance prescription and illicit stimulant NPDS cases. For CII prescription stimulant NPDS exposure cases, 16.9% also involved use of prescription or illicit opioids and 9% also involved use of cannabis, while for illicit stimulant NPDS exposure cases, 35.4% and 14.9% also involved use of prescription or illicit opioids and cannabis, respectively.

Polysubstance use among cases of CII prescription stimulant NMU was also stratified by prescription stimulant API. Out of 12,659 multi-substance NMU NPDS exposure cases involving CII prescription stimulants and other substances, amphetamine sulfate products were involved in only 8 cases, with 75% of those cases involving additional use of either prescription or illicit opioids or any benzodiazepine (**Table 35**). Overall, mixed amphetamine salt products were the most commonly involved CII prescription stimulant API in multi-substance NMU NPDS cases, and alcohol, benzodiazepines, and prescription or illicit opioids were the most common substances used along with mixed amphetamine salt products at the time of the PCC call that generated the NPDS exposure case.

Table 35. National Poison Data System exposure cases involving NMU of prescription and illicit stimulants, by other substance exposures, 2001 to 2018

Stimulants	Overall Cases				Polysubstance Exposures - Multi-Substance Cases*											
	Single-Substance Cases		Multi-Substance Cases		Any Opioid**		Any Benzodiazepine		Any Muscle Relaxant		Any Alcohol		Any Cannabis		Any Illicit Stimulant	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
CII Rx Stimulants [†] (excluding regulated pharmaceutical cocaine)	22,070	63.5%	12,659	36.5%	2,140	16.9%	2,429	19.2%	338	2.7%	2,957	23.4%	1,140	9.0%	860	6.8%
Amphetamine	22	73.3%	8	26.7%	2	25.0%	4	50.0%	0	0.0%	0	0.0%	1	12.5%	1	12.5%
Dextroamphetamine	419	59.3%	288	40.7%	50	17.4%	62	21.5%	14	4.9%	49	17.0%	20	6.9%	15	5.2%
Mixed Amphetamine Salts	11,383	60.6%	7,398	39.4%	1,392	18.8%	1,581	21.4%	207	2.8%	1,836	24.8%	707	9.6%	605	8.2%
Lisdexamfetamine	2,525	63.6%	1,446	36.4%	157	10.9%	214	14.8%	27	1.9%	243	16.8%	141	9.8%	66	4.6%
Methylphenidate	6,952	64.7%	3,801	35.3%	558	14.7%	576	15.2%	96	2.5%	837	22.0%	273	7.2%	192	5.1%
Dexmethylphenidate	708	67.1%	347	32.9%	34	9.8%	45	13.0%	6	1.7%	46	13.3%	20	5.8%	6	1.7%
Methamphetamine (Rx only)	61	59.8%	41	40.2%	12	29.3%	11	26.8%	0	0.0%	3	7.3%	7	17.1%	4	9.8%
Any Illicit Stimulant	48,512	54.7%	40,117	45.3%	14,198	35.4%	7,829	19.5%	1,154	2.9%	9,613	24.0%	5,975	14.9%		
Cocaine	26,055	48.1%	28,067	51.9%	10,074	35.9%	5,780	20.6%	862	3.1%	7,932	28.3%	4,508	16.1%		
Methamphetamine (Illicit)	22,457	62.0%	13,786	38.0%	4,521	32.8%	2,294	16.6%	315	2.3%	1,911	13.9%	1,734	12.6%		
Amphetamine (NOS)	5,078	48.4%	5,403	51.6%	1,386	25.7%	1,105	20.5%	153	2.8%	1,045	19.3%	1,139	21.1%		

CII, Schedule II; Rx, Prescription; NOS, Not otherwise specified.

Note: ‘†’ indicates CII stimulants only. Prescription stimulants include amphetamine, dextroamphetamine, amphetamine mixed salts, lisdexamfetamine, methylphenidate, dexmethylphenidate, and methamphetamine. Regulated pharmaceutical cocaine and stimulants indicated for weight-loss (e.g., phentermine) are not included.

Note: Reports of regulated pharmaceutical and illicit cocaine exposures are considered together.

Note: Amphetamine exposures not referencing a specific prescription or illicit product are considered “Amphetamine (NOS).”

Note: NMU consists of “Intentional – Misuse” and “Intentional – Abuse” exposures.

Note: Excludes prescription and illicit stimulant exposure cases with “Intentional - Suspected Suicide” and “Intentional - Unknown” reasons.

Note: Children 5 years and younger are not included.

Note: Percentages for each substance are calculated using the total Multi-Substance NPDS cases for each stimulant category.

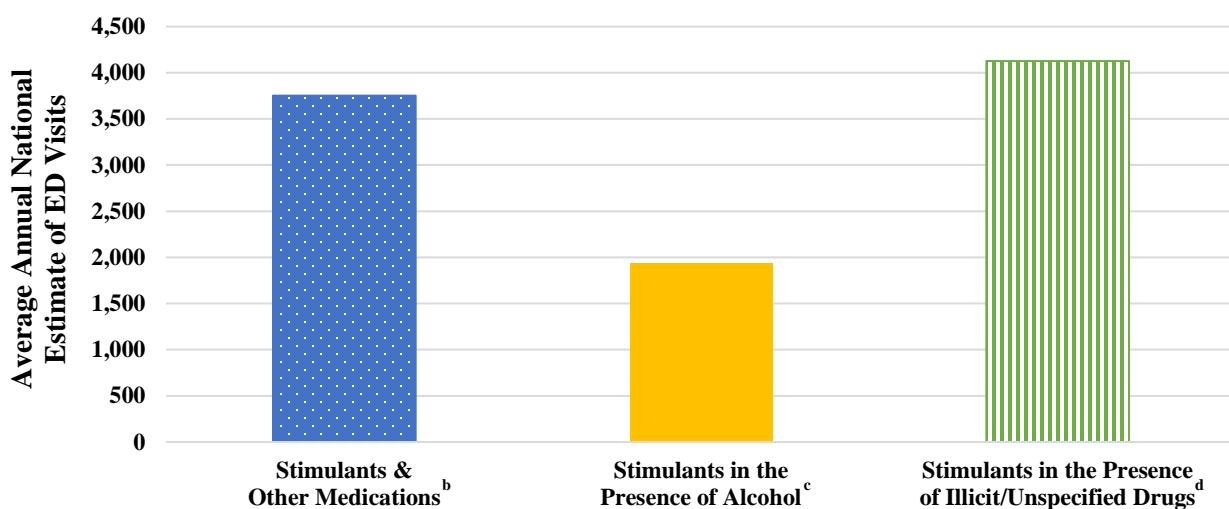
Note: ‘**’ The counts of each polysubstance exposure are not mutually exclusive.

Note: ‘***’ Excludes N = 22 exposure cases where polysubstance prescription opioid or illicit opioid exposure could not be determined.

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

Data from NEISS-CADES were also used to assess polysubstance use among people with ED visits in the United States for harms from NMU of prescription stimulants. From 2016 through 2018, an estimated 4,127 annual ED visits for harms involving NMU of prescription stimulants had documented concurrent use of illicit or unspecified drugs, an estimated 3,752 annual ED visits for harms involving NMU of prescription stimulants also had use of other medications, and an estimated 1,936 annual ED visits for harms involving NMU of prescription stimulants also had documented concurrent use of alcohol (**Figure 58**). Polysubstance use among people with ED visits in the United States for harms involving NMU of prescription stimulants were further analyzed by specific drugs and other substances. **Figure 59** shows that among 2016 to 2018 ED visits in the United States due to harms involving NMU of prescription stimulants in which concurrent substance use was documented, the most commonly documented substances included marijuana (2,532 estimated annual visits), benzodiazepines (2,180 estimated annual visits), alcohol (1,936 estimated annual visits), prescription opioid analgesics (1,276 estimated annual visits), and cocaine (1,191 estimated annual visits).

Figure 58. National estimates of emergency department visits due to adverse events involving NMU^a of prescription stimulants with other documented concurrent substances: NEISS-CADES, 2016 to 2018



ED, emergency department; NEISS-CADES, National Electronic Injury Surveillance System – Cooperative Adverse Drug Event Surveillance; NMU, nonmedical use.

Note: ‘a’ includes abuse, therapeutic misuse, and overdoses without documentation of therapeutic intent, self-harm, abuse, or misuse.

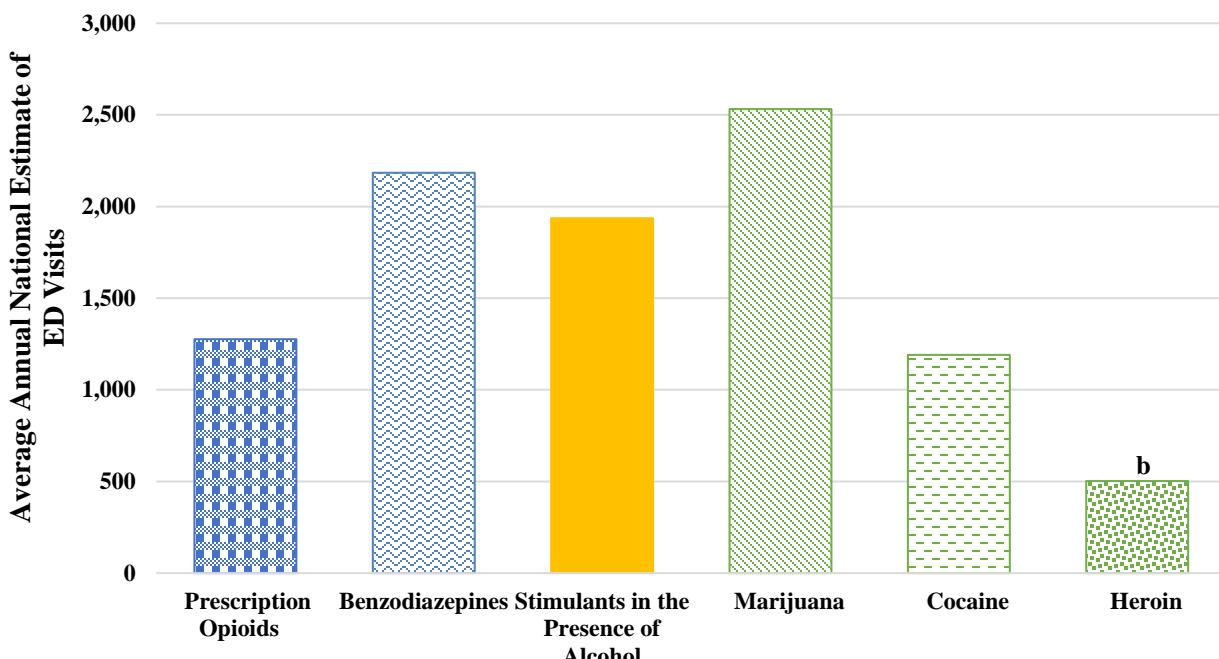
Note: ‘b’ alcohol and illicit/unspecified drugs may also be involved.

Note: ‘c’ medications and illicit/unspecified drugs may also be involved.

Note: ‘d’ medications and alcohol may also be involved.

Source: FDA-generated figure. National Electronic Injury Surveillance System – Cooperative Adverse Drug Event Surveillance (NEISS-CADES) project, Centers for Disease Control and Prevention.

Figure 59. National estimates of emergency department visits due to adverse events involving NMU^a of prescription stimulants and other documented concurrent substances: NEISS-CADES, 2016 to 2018



AE, adverse event; CV, coefficient of variation; ED, emergency department; NEISS-CADES, National Electronic Injury Surveillance System – Cooperative Adverse Drug Event Surveillance; NMU, nonmedical use.

Note: Some ED visits may have involved >1 of the substances listed (e.g., other medications, alcohol, illicit/unspecified drugs).

Note: National estimates of ED visits due to AEs involving prescription stimulants with antidepressants, non-benzodiazepine sedative hypnotics, antipsychotics, skeletal muscle relaxants, anticonvulsants, and centrally-acting anti-adrenergics are considered statistically unstable due to <20 cases for each and are not shown.

Note: National estimates of ED visits due to AEs involving prescription stimulants with unspecified opioid, methamphetamine, unspecified amphetamine, and illicit fentanyl are considered statistically unstable due to <20 cases for each and are not shown.

Note: ‘a’ includes abuse, therapeutic misuse, and overdoses without documentation of therapeutic intent, self-harm, abuse, or misuse.

Note: ‘b’ indicates the estimate has a coefficient of variation >30% (CV = 31%) and may be statistically unstable.

Source: FDA-generated figure. National Electronic Injury Surveillance System – Cooperative Adverse Drug Event Surveillance (NEISS-CADES) project, Centers for Disease Control and Prevention.

3.2.7 Trajectory of Stimulant NMU

3.2.7.1 Trajectory of NMU Within the General Population

Among the 12,000 respondents of the Applicant-submitted general population survey, AR19.MA004, 6.4% (n=762) reported lifetime NMU of prescription stimulants (**Figure 11, shown previously**). Of those 762 respondents, 10.2% (n=78) reported only NMU of prescription stimulants, the other 89.8% (n=684) reported lifetime NMU of illicit drugs and/or opioids in addition to prescription stimulants (**Table 36**).

Among those that reported lifetime NMU of more than just prescription stimulants, 29.2% of respondents initiated their NMU of drugs with a prescription stimulant (**Table 37**). Illicit drugs were the most common drug of initiation reported by those with lifetime NMU of prescription stimulants (65.2%). Specifically, marijuana was the most common first illicit drug reported by respondents with a lifetime history of NMU of prescription stimulants (**Table 38**). As a comparison, 17.1% of respondents with lifetime NMU of prescription stimulants initiated with prescription opioid analgesics.

Table 36. Pathway of drug use initiation for those with lifetime NMU of a single drug type, among people aged 18 to 49 years, AR19.MA004, an online survey of the general U.S. population conducted by the internet panel company YouGov

NMU Among Users of 1 of 3 Drug Types (N=4,403)	n	%
Illicit drugs only	3,701	84.1
Prescription opioids only	624	14.2
Prescription stimulants only	78	1.8

NMU, nonmedical use; U.S., United States.

Source: Nonmedical Use of Prescription Medications among the General Population (AR19.MA004). Results from Table 52. Pathways of initiation of prescription stimulant NMU, prescription opioid NMU, and use of illicit drugs among respondents who reported using only one of the three specified drug types.

Table 37. Initial drug type for those with lifetime NMU of a multiple drug types, among people aged 18 to 49 years, AR19.MA004, an online survey of the general U.S. population conducted by the internet panel company YouGov

First Drug of Initiation in Multi-Drug Use Pathways (2 or 3 Drug Types)	All Multi-Drug Pathways N=1,711		Multi-drug Pathways Involving Prescription Stimulant NMU N=684	
	n	%*	n	%*
Illicit drugs	1,284	75.0	446	65.2
Prescription opioids	343	20.0	117	17.1
Prescription stimulants	200	11.7	200	29.2

NMU, nonmedical use; U.S., United States.

Note: '*' indicate column does not add to 100% because respondents could endorse more than one first drug of NMU.

Source: Nonmedical Use of Prescription Medications among the General Population (AR19.MA004). Results from Table 58. First drug of initiation in multi-drug use pathways (two or three specified drug types reported).

Table 38. Initial illicit drug used for those multi-drug use pathways involving NMU of a prescription stimulant, among people aged 18 to 49 years, AR19.MA004, an online survey of the general U.S. population conducted by the internet panel company YouGov

First Illicit Drug of Initiation	Pathway of multi-drug use that involved prescription stimulant NMU N=575	
	n	%
Marijuana	440	76.5
Multiple illicit drugs	65	11.3
Inhalants	15	2.6
Cocaine or crack	11	1.9
Amphetamines/methamphetamines	10	1.7
Heroin	9	1.6
Hallucinogens	9	1.6
Other illicit substance	8	1.4
Street fentanyl	4	0.7
Barbiturates	4	0.7

NMU, nonmedical use; U.S., United States.

Source: Nonmedical Use of Prescription Medications among the General Population (AR19.MA004). Results from Table 61. First illicit drug of initiation in pathways of multi-drug use that involved prescription stimulant NMU.

Among the 225 respondents of AR19.MA008 with lifetime NMU of prescription stimulants via a non-oral route, 98.7% (N=222) also reported lifetime illicit drug use. Of those 222 respondents, 82.0%

(N=182) reported using an illicit drug prior to prescription stimulants (**Table 39**), with the most common illicit drug reported being marijuana (**Table 40**). On average respondents in this study reported being 15.9 years of age at the time of their initial marijuana use, while respondents were, on average, 18.7 years of age at the time of their first NMU of a prescription stimulant (**Table 41**).

Table 39. First drug type of initiation in multi-drug use pathways, AR19.MA008, an online survey of adult Reddit users aged 18 years or older with a history of non-oral prescription stimulant use

First Drug of Initiation in Multi-Drug Use Pathways (2 Drug Types)	Multi-Drug Pathways (N=222)	
	n	%
Illicit drugs	182	82.0
Prescription stimulants	40	18.0

Source: Understanding the Patterns of Prescription Medication Abuse and Progression to Non-Oral Routes of Administration (AR19.MA008). Results from Table 66. First drug of initiation in multi-drug use pathways (two specified drug types reported).

Table 40. Pathway of drug initiation, AR19.MA008, an online survey of Reddit users aged 18 years or older with a history of non-oral prescription stimulant use

Pathway of Initiation of NMU Among Users of Both Drug Types (N=222)*	n	%
Marijuana → prescription stimulants	173	77.9
Prescription stimulants → marijuana	32	14.4
Cocaine or crack → prescription stimulants	4	1.8
Inhalants → prescription stimulants	2	0.9
Hallucinogens → prescription stimulants	2	0.9
Prescription stimulants → cocaine or crack	2	0.9
Prescription stimulants → barbiturates	2	0.9
Amphetamines/methamphetamines → prescription stimulants	1	0.5
Prescription stimulants → heroin	1	0.5
Prescription stimulants → inhalants	1	0.5
Prescription stimulants → amphetamines/methamphetamines	1	0.5
Prescription stimulants → hallucinogens	1	0.5

NMU, Nonmedical Use.

Note: ** indicates 222 respondents had prescription stimulant NMU and illicit drug use.

Source: Understanding the Patterns of Prescription Medication Abuse and Progression to Non-Oral Routes of Administration (AR19.MA008). Results from Table 65. Pathways of initiation of prescription stimulant NMU and use of illicit drugs among respondents who reported using both specified drug types.

Table 41. Average age of prescription stimulant NMU and illicit drug use, AR19.MA008, an online survey of Reddit users aged 18 years or older with a history of non-oral prescription stimulant use

Drug	N	Mean	Standard Deviation
Prescription stimulant	225	18.7	3.7
Marijuana	221	15.9	2.5
Barbiturates	25	17.8	2.8
Hallucinogens	115	18.1	2.3
Inhalants	45	18.2	4.2
Cocaine or crack	136*	19.7	3.3
Amphetamines	82	20.1	4.6
Other illicit drug	17	20.4	3.7
Heroin	35	20.9	5.5
Street fentanyl	13	22.8	5.1

NMU, nonmedical use.

Note: ** indicates one respondent was missing information on age.

Source: Understanding the Patterns of Prescription Medication Abuse and Progression to Non-Oral Routes of Administration (AR19.MA008). Results from Table 71. Mean age at initiation of prescription stimulant NMU and illicit drug use.

Data collected from the NOMAD survey suggested 79.8% of respondents had prior or concurrent substance use with their first non-oral prescription ADHD stimulant NMU event (**Table 42**). Among those that reported prior substance use, marijuana was the most common substance reported (86.2%), followed by prescription painkillers (36.9%), benzodiazepines (34.7%) and cocaine (27.3%) (**Table 43**).

Table 42. Substance use pathways prior and after non-oral prescription stimulant NMU event, NOMAD, an online survey of adults aged 18 years or older with a history of NMU of prescription ADHD stimulants via a non-oral route

	No ADHD Dx (N=430)	ADHD Dx (N=575)	All Subjects (N=1005)
Pathway prior to non-oral abuse			
n	430	575	1005
No prior substance use	97 (22.6%)	106 (18.4%)	203 (20.2%)
Oral stimulant use only	140 (32.6%)	190 (33.0%)	330 (32.8%)
Other substance use only	74 (17.2%)	110 (19.1%)	184 (18.3%)
Other substance use then oral stimulant use	90 (20.9%)	140 (24.3%)	230 (22.9%)
Oral stimulant use then other substance use	12 (2.8%)	12 (2.1%)	24 (2.4%)
Oral stimulant use and other substance use started concurrently	17 (4.0%)	17 (3.0%)	34 (3.4%)
Pathways following non-oral abuse			
n	430	575	1005
Previously used other substances; Halted non-oral stimulant abuse	11 (2.6%)	29 (5.0%)	40 (4.0%)
Initiated other substance use; Halted non-oral stimulant abuse	2 (0.5%)	6 (1.0%)	8 (0.8%)
Halted non-oral stimulant abuse; no prior history of other substance use; no new substance use	14 (3.3%)	26 (4.5%)	40 (4.0%)
Previously used other substances; Continued non-oral stimulant abuse	182 (42.3%)	250 (43.5%)	432 (43.0%)
Initiated other substance use; Continued non-oral stimulant abuse	53 (12.3%)	108 (18.8%)	161 (16.0%)
Continued non-oral stimulant abuse; no prior history of other substance use; no new substance use	168 (39.1%)	156 (27.1%)	324 (32.2%)

ADHD, Attention Deficit Hyperactivity Disorder; Dx, diagnosis; NMU, nonmedical use.

Note: 'Other substance abuse' indicates illicit use of prescription drugs (excluding ADHD products) and illicit drugs, but not nicotine and alcohol.

Source: The NOMAD Non-Oral Abuse Survey: Elucidation of Pathways to Non-Oral ADHD Prescription Stimulant Abuse (NOMAD). Results from Table 14.2.4 Substance Use Pathways Before and After Non-Oral Abuse.

Table 43. Other substance use prior to non-oral prescription stimulant NMU event, NOMAD, an online survey of adults aged 18 years or older with a history of NMU of prescription ADHD stimulants via a non-oral route

	No ADHD Dx (N=430)	ADHD Dx (N=575)	All Subjects (N=1005)
Before the first time you non-orally abused a prescription ADHD stimulant, did you use or consume any other kind of substance(s), including illicit drugs, marijuana, alcohol or nicotine?			
n	430	575	1005
Yes	270 (62.8%)	367 (63.8%)	637 (63.4%)
No	160 (37.2%)	208 (36.2%)	368 (36.6%)
What other types of substances did you use or consume during that time?			
n	270	367	637
Other prescription medications	61 (22.6%)	112 (30.5%)	173 (27.2%)
Alcohol	161 (59.6%)	262 (71.4%)	423 (66.4%)
Cigarettes, Vaporizers, E-Cigarettes, Chewing Tobacco, or some other type of nicotine product	167 (61.9%)	271 (73.8%)	438 (68.8%)
Illicit drugs of any kind, including marijuana	174 (64.4%)	255 (69.5%)	429 (67.3%)
Other	4 (1.5%)	2 (0.5%)	6 (0.9%)
You mentioned that you used or consumed some other prescription medication(s) as not intended and/or some kind of illicit drug(s) prior to the first time you non-orally abused a prescription ADHD stimulant. Which of the following substances did you use?			
n	193	279	472
Marijuana	161 (83.4%)	246 (88.2%)	407 (86.2%)
Heroin (including illicit fentanyl)	17 (8.8%)	24 (8.6%)	41 (8.7%)
Cocaine	43 (22.3%)	86 (30.8%)	129 (27.3%)
Methamphetamines	32 (16.6%)	53 (19.0%)	85 (18.0%)
MDMA, or Ecstasy	33 (17.1%)	60 (21.5%)	93 (19.7%)
Ketamine	14 (7.3%)	15 (5.4%)	29 (6.1%)
LSD	30 (15.5%)	36 (12.9%)	66 (14.0%)
Prescription painkillers (opioids) or other illicit opioids	67 (34.7%)	107 (38.4%)	174 (36.9%)
Benzodiazepines (e.g., Xanax, Valium, etc.)	58 (30.1%)	106 (38.0%)	164 (34.7%)
Sedatives (e.g., Benadryl)	30 (15.5%)	45 (16.1%)	75 (15.9%)
Other	4 (2.1%)	13 (4.7%)	17 (3.6%)

ADHD, Attention Deficit Hyperactivity Disorder; Dx, diagnosis; LSD, Lysergic acid diethylamide; MDMA, 3,4-Methylenedioxymethamphetamine; NMU, nonmedical use.

Source: The NOMAD Non-Oral Abuse Survey: Elucidation of Pathways to Non-Oral ADHD Prescription Stimulant Abuse (NOMAD). Results from Table 14. Other Substance Abuse Behavior Prior to Non-Oral Abuse.

3.2.7.2 Transition Between Routes

Among respondents in AR19.MA008 with lifetime NMU of prescription stimulants via multiple routes, 89.1% reported an oral route as the initial route of NMU of prescription stimulants, followed by 10.9% of respondents that initiated with snorting (**Table 44**). The most common initial non-oral route among respondents reporting multiple routes was snorting (97.9%), while a relatively small percentage of respondents reported non-oral initiation of prescription stimulants via smoking or injection (2.1%) (**Table 45**). Data from the NOMAD survey, which included people with a history of NMU of an ADHD prescription stimulant via a non-oral route, showed that 61.5% of respondents nonmedically used a prescription stimulant orally prior to their first non-oral use event (**Table 42, shown previously**).

Table 44. First route of administration used for NMU of prescription stimulants, among adults with lifetime NMU of prescription stimulants via multiple routes of administration, AR19.MA008, an online survey of adult Reddit users aged 18 years or older with a history of non-oral prescription stimulant use

First Route of Administration for NMU Among Respondents Reporting Multiple Routes of Administration (N=193)*	n	%
Swallowed	172	89.1
Snorted	21	10.9
Injected	-	-
Smoked/vaped	-	-

NMU, nonmedical use.

Note: * indicates only respondents who reported multiple routes of administration for prescription stimulant NMU are included. These data are limited to those whose first route was either swallowed, snorted, injected, or smoked/vaped. Those whose first route was “other route” were excluded.

Source: Understanding the Patterns of Prescription Medication Abuse and Progression to Non-Oral Routes of Administration (AR19.MA008). Results from Table 69. First route of administration for prescription stimulant NMU among respondents reporting multiple routes of administration for prescription stimulant NMU.

Table 45. First non-oral route of administration used for NMU of prescription stimulants, among adults with lifetime NMU of prescription stimulants via multiple routes of administration, AR19.MA008, an online survey of adult Reddit users aged 18 years or older with a history of non-oral prescription stimulant use

First Non-Oral Route of Administration for NMU Among Respondents Reporting Multiple Routes of Administration (N=194)*	n	%
Snorted	190	97.9
Smoked/vaped	3	1.6
Injected	1	0.5

NMU, nonmedical use.

Note: * indicates only respondents who reported multiple routes of administration for prescription stimulant NMU, including at least one non-oral route, are included.

Source: Understanding the Patterns of Prescription Medication Abuse and Progression to Non-Oral Routes of Administration (AR19.MA008). Results from Table 70. First non-oral route of administration for prescription stimulant NMU among respondents reporting multiple routes of administration for prescription stimulant NMU.

3.2.8 Morbidity Associated with NMU of Prescription Stimulants

3.2.8.1 Epidemiology Data

3.2.8.1.1 General U.S. Population Studies

SUDs are an important potential adverse clinical outcome associated with the use and NMU of prescription drugs. SUDs can occur when the recurrent use of alcohol and/or drugs causes clinically and functionally significant impairment, such as health problems, disability, and failure to meet major responsibilities at work, school, or home. According to the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5), a diagnosis of SUD is based on evidence of impaired control, social impairment, risky use, and pharmacological criteria. Symptoms of stimulant use disorders include craving for stimulants, failure to control use when attempted, continued use despite interference with major obligations or social functioning, use of larger amounts over time, development of tolerance, spending a great deal of time to obtain and use stimulants, and withdrawal symptoms that occur after stopping or

reducing use, including fatigue, vivid and unpleasant dreams, sleep problems, increased appetite, or irregular problems in controlling movement.³⁴

NSDUH provides some limited prevalence data on a range of SUDs, including prescription stimulants.³⁵ The most recent available year of data from NSDUH (2018) estimated 561,000 people aged 12 years or older had a stimulant use disorder, corresponding to approximately 0.2% of the population. The highest prevalence of stimulant use disorder was observed among individuals between the ages of 18 to 25 years with an estimated 185,000 individuals, corresponding to 0.5% of the population.

3.2.8.1.2 People Seeking Advice or Healthcare

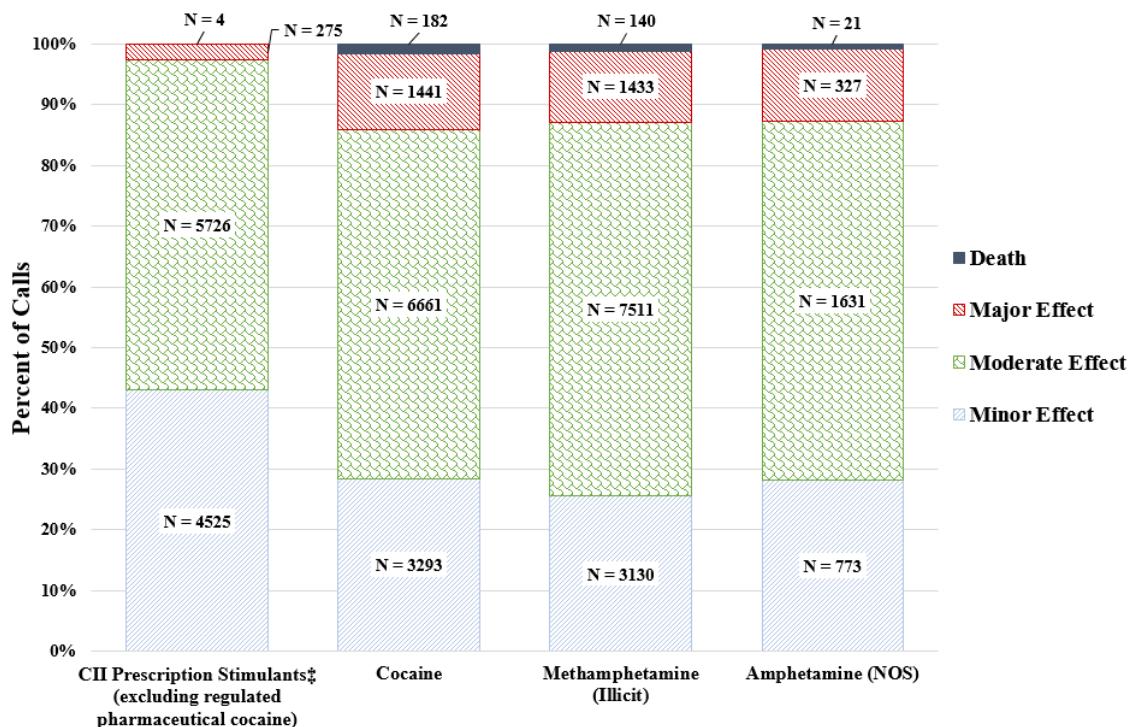
Adverse medical and clinical outcomes associated with NMU of prescription and illicit stimulants are dependent on a multitude of factors and vary in type and severity based on those factors. While epidemiologic data are limited, there are a few resources available that can provide information on harms associated with NMU of prescription and illicit stimulants.

One such data source is AAPCC NPDS. While NPDS generally does not capture unattended and out of hospital deaths, NPDS data do capture medical outcome severity and clinical effects related to specific exposures for cases where this information is provided during initial or follow-up calls. Between 2001 and 2018, more than 95% of NPDS exposure cases for single-substance NMU of CII prescription stimulants documented either a minor or moderate effect from the exposure, with 45% of cases having only minor effects resulting from the exposure, and fewer than 3% of cases with major effects from the exposure (**Figure 60**). This contrasts with cocaine, illicit methamphetamine, and amphetamine NOS exposure cases. For these stimulants, fewer than 30% of single-substance NMU NPDS exposure cases with a related medical outcome documented minor effects from the exposure, and more than 10% of cases documented major effects from the exposure.

³⁴ Substance Abuse and Mental Health Services Administration: Substance Use Disorders. Available at: <https://www.samhsa.gov/disorders/substance-use> (accessed August 27, 2020).

³⁵ National Survey on Drug Use and Health (NSDUH). 2018 Annual National Report. Available at: <https://www.samhsa.gov/data/report/2018-nsduh-annual-national-report> (accessed August 27, 2020)

Figure 60. National Poison Data System single-substance exposure cases involving NMU of prescription and illicit stimulants, by related medical outcome, 2001 to 2018



NMU, nonmedical use; CII, Schedule II; NOS, Not otherwise specified.

Note: ‘†’ indicates CII stimulants only. Prescription stimulants include amphetamine, dextroamphetamine, amphetamine mixed salts, lisdexamfetamine, methylphenidate, dextroamphetamine, and methamphetamine. Regulated pharmaceutical cocaine and stimulants indicated for weight-loss (e.g., phentermine) are not included.

Note: Reports of regulated pharmaceutical and illicit cocaine exposures are considered together.

Note: Amphetamine exposures not referencing a specific prescription or illicit product are considered "Amphetamine (NOS)."

Note: NMU consists of "Intentional – Misuse" and "Intentional – Abuse" exposures.

Note: Includes single-substance, related medical outcome, prescription and illicit stimulant exposure cases only.

Note: Excludes prescription and illicit stimulant exposure cases with "Intentional - Suspected Suicide" and "Intentional - Unknown" reasons.

Note: Excludes prescription and illicit stimulant exposure cases with Medical Outcomes "Not/Unable to Follow" (N = 13726) and "Unrelated Effect" (N = 45).

Note: Children 5 years and younger are not included.

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

Table 46 shows that from 2001 through 2018, the top three related clinical outcomes for single-substance prescription stimulant, cocaine, and illicit methamphetamine NPDS exposure cases that had a medical outcome related to the exposure were tachycardia, agitation, and hypertension, although these three related clinical effects were documented in a higher percentage of illicit methamphetamine cases (67.2%, 51.4%, and 30.6%, respectively) than for CII prescription stimulant (58.0%, 37.6%, and 23.3%, respectively) and cocaine cases (54.2%, 28.5%, and 26.6%, respectively). Four of the top ten related clinical outcomes for single-substance cocaine and illicit methamphetamine NMU NPDS cases were the same and were not one of the top ten related clinical outcomes for single-substance CII prescription stimulant NMU cases. These clinical outcomes include elevated creatine phosphokinase, diaphoresis, fever/hyperthermia, and confusion.

Table 46. National Poison Data System single-substance exposure cases involving NMU of prescription and illicit stimulants, by top ten clinical outcomes, 2001 to 2018

CII Prescription Stimulants [‡] (excluding regulated pharmaceutical cocaine) N = 10,530		Cocaine N = 11,577		Methamphetamine (Illicit) N = 12,214	
Clinical Outcome	% of Total Cases	Clinical Outcome	% of Total Cases	Clinical Outcome	% of Total Cases
Tachycardia	58.0%	Tachycardia	54.2%	Tachycardia	67.2%
Agitation	37.6%	Agitation	28.5%	Agitation	51.4%
Hypertension	23.3%	Hypertension	26.6%	Hypertension	30.6%
Other - Miscellaneous	21.5%	Chest pain (including noncardiac)	13.9%	Other - Miscellaneous	16.1%
Chest pain (including noncardiac)	7.7%	Other - Miscellaneous	13.4%	Hallucinations/delusions	12.0%
Tremor	7.6%	Drowsiness/lethargy	8.5%	Confusion	11.5%
Hallucinations/delusions	7.1%	CPK elevated	7.2%	CPK elevated	10.8%
Nausea	6.8%	Diaphoresis	5.9%	Diaphoresis	10.5%
Mydriasis	6.3%	Fever/hyperthermia	5.8%	Tremor	9.8%
Dizziness/vertigo	5.4%	Confusion	5.7%	Fever/hyperthermia	9.7%

CII, Schedule II; CPK, creatinine phosphokinase; NMU, nonmedical use.

Note: ‘‡’ indicates CII stimulants only. Prescription stimulants include amphetamine, dextroamphetamine, amphetamine mixed salts, lisdexamfetamine, methylphenidate, dexmethylphenidate, and methamphetamine. Regulated pharmaceutical cocaine and stimulants indicated for weight-loss (e.g., phentermine) are not included.

Note: Reports of regulated pharmaceutical and illicit cocaine exposures are considered together.

Note: NMU consists of “Intentional – Misuse” and “Intentional – Abuse” exposures.

Note: Includes single-substance, related clinical outcome, prescription and illicit stimulant exposure cases only.

Note: Excludes prescription and illicit stimulant exposure cases with “Intentional - Suspected Suicide” and “Intentional - Unknown” reasons.

Note: Includes the ten most common single-substance, related clinical outcomes in prescription and illicit stimulant exposure cases.

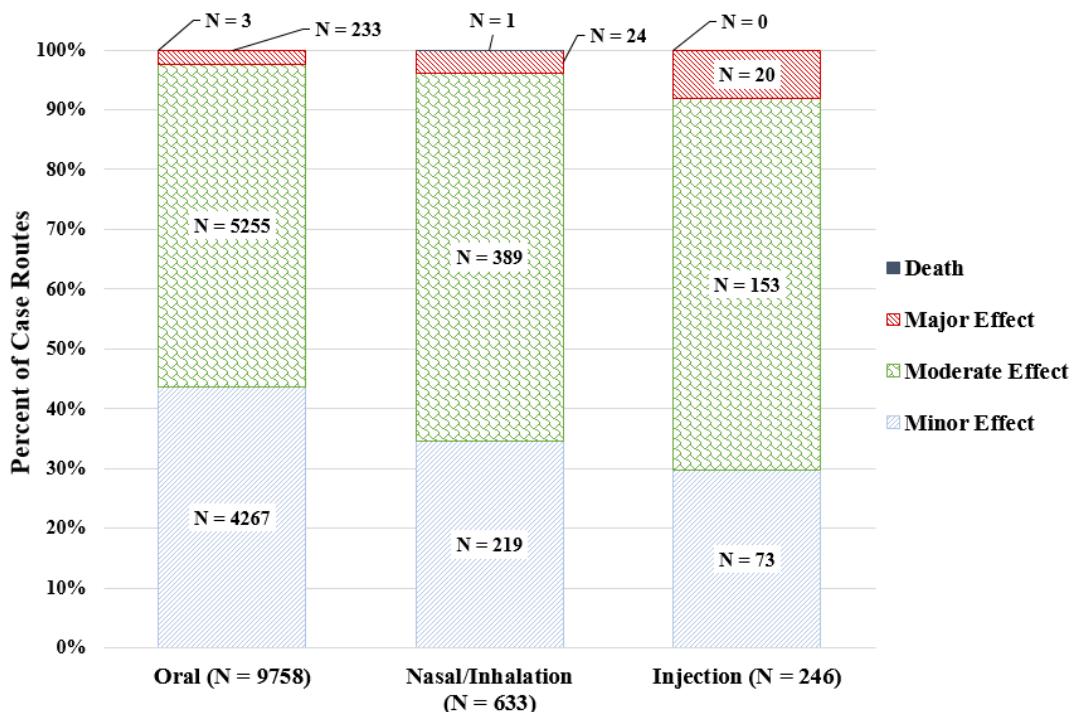
Note: Children 5 years and younger are not included.

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

Adverse health outcomes associated with NMU of prescription stimulants appeared to vary by route in NPDS data. From 2001 through 2018, among single-substance NMU cases in NPDS that involved CII prescription stimulants, approximately 70% of injection route mentions had a related medical outcome with a moderate or major effect, while approximately 65% of nasal/inhalation and approximately 56% of oral route mentions had a related medical outcome with a moderate or major effect (**Figure 61**).³⁶ Although moderate or major health effects were noted for a greater proportion of exposure cases that mentioned injection or nasal/inhalation routes compared to oral routes, almost 90% of the total route mentions with more severe medical outcomes (moderate and major effects) were in NPDS cases involving an oral route of exposure.

³⁶ Multiple routes can be mentioned during one case, so we considered differences in adverse health outcomes by route mention.

Figure 61. National Poison Data System single-substance exposure cases involving NMU of CII prescription stimulants[‡] (excluding regulated pharmaceutical cocaine), by route and medical outcome, 2001 to 2018



CII, Schedule II; NMU, nonmedical use.

Note: ‘‡’ indicates CII stimulants only. Prescription stimulants include amphetamine, dextroamphetamine, amphetamine mixed salts, lisdexamfetamine, methylphenidate, dexmethylphenidate, and methamphetamine. Regulated pharmaceutical cocaine and stimulants indicated for weight-loss (e.g., phentermine) are not included.

Note: Includes single-substance, related medical outcome prescription stimulant exposure cases only.

Note: NMU consists of “Intentional – Misuse” and “Intentional – Abuse” exposures.

Note: Excludes prescription stimulant exposure cases with “Intentional - Suspected Suicide” or “Intentional - Unknown” reasons.

Note: Excludes prescription stimulant exposure cases with Medical Outcomes “Not/Unable to Follow” (N = 3888) and “Unrelated Effect” (N = 7).

Note: Total route of exposure mentions for the routes “Other - aspiration, bite/sting, dermal, ocular, other, otic, rectal, and vaginal” (N = 40) and “Unknown” (N = 21) are not included in this figure.

Note: Children 5 years and younger are not included.

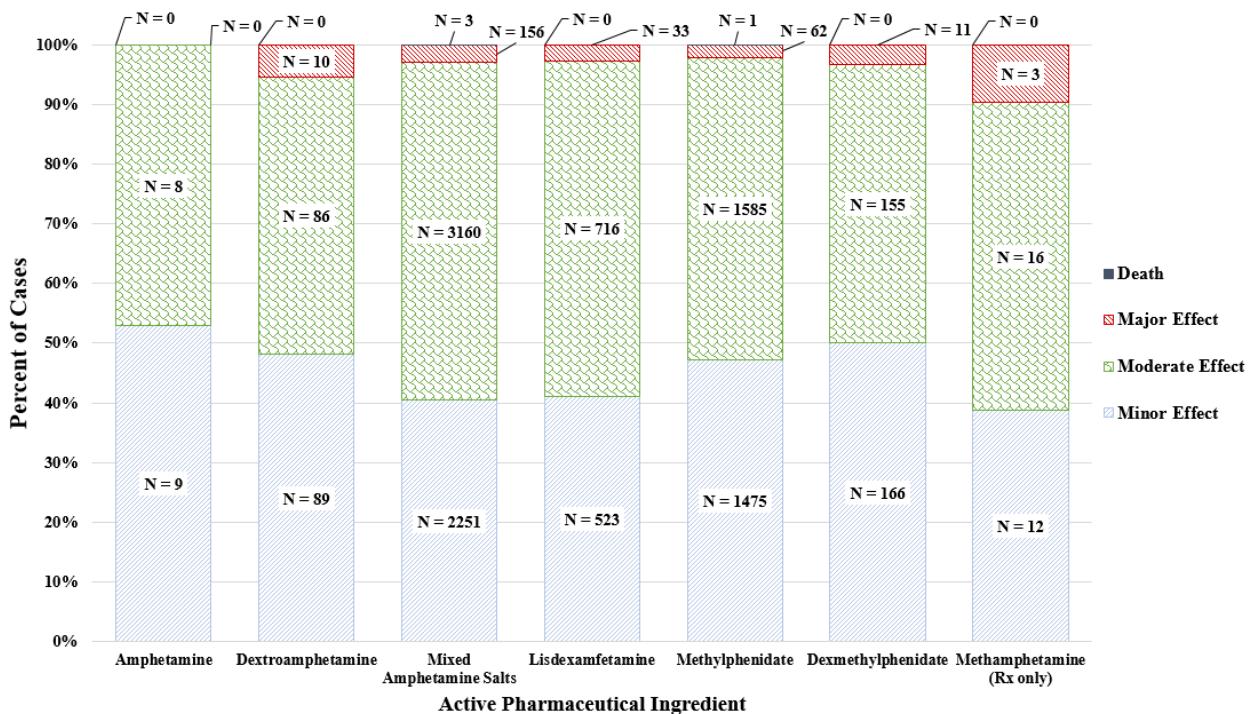
Note: Routes are represented as percentage of total route of misuse/abuse mentions for prescription stimulants.

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

CII prescription stimulant single-substance NMU NPDS exposure cases were further stratified by API to explore medical outcome severity and clinical effects related to exposures to specific stimulant APIs.

Figure 62 shows that from 2001 through 2018, the percentage of NMU NPDS cases resulting in each related medical outcome for each stimulant API was very similar to the overall prescription stimulant category, while the percentage of related medical outcomes for prescription methamphetamine cases was similar to illicit methamphetamine NPDS cases, as previously shown in **Figure 60, above**.

Figure 62. Medical outcomes in National Poison Data System single-substance exposure cases involving NMU of CII prescription stimulants, by API, 2001 to 2018



API, active pharmaceutical ingredient; NMU, nonmedical use; Rx, prescription.

Note: Schedule II stimulants only.

Note: Reports of regulated pharmaceutical and illicit cocaine exposures are considered together and are therefore excluded.

Note: Amphetamine exposures not referencing a specific prescription or illicit product are considered "Amphetamine (not otherwise specified)," and are also excluded.

Note: Includes single-substance, related medical outcome, prescription stimulant exposure cases only.

Note: NMU consists of "Intentional – Misuse" and "Intentional – Abuse" exposures.

Note: Excludes prescription stimulant exposure cases with "Intentional - Suspected Suicide" and "Intentional - Unknown" reasons.

Note: Excludes prescription stimulant exposure cases with Medical Outcomes "Not/Unable to Follow" (Amphetamine: N = 2, Dextroamphetamine: N = 71, Mixed Amphetamine Salts: N = 2254, Lisdexamfetamine: N = 381, Methylphenidate: N = 1069, Dexmethylphenidate: N = 99, Methamphetamine: N = 12) and "Unrelated Effect" (Amphetamine: N = 0, Dextroamphetamine: N = 0, Mixed Amphetamine Salts: N = 4, Lisdexamfetamine: N = 1, Methylphenidate: N = 2, Dexmethylphenidate: N = 0, Methamphetamine: N = 0).

Note: Children 5 years and younger are not included.

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

The top four related clinical outcomes during the aggregated eighteen-year period for single-substance CII prescription stimulant APIs that had a medical outcome related to the exposure were tachycardia, agitation, hypertension, and other – miscellaneous, except for single amphetamine sulfate products, which had a higher percentage of NPDS exposure cases with related chest pain (including noncardiac) or vomiting and a lower percentage of NPDS exposure cases resulting in hypertension when compared to other prescription stimulant APIs (**Table 47**). Overall, the top ten clinical outcomes related to single-substance NMU NPDS cases for each CII prescription stimulant API were very similar to the entire prescription stimulant category, as shown in **Table 46, above**.

Table 47. Top ten clinical outcomes in National Poison Data System single-substance exposure cases involving NMU of prescription stimulants, by API, 2001 to 2018.

Amphetamine N = 17		Dextroamphetamine N = 185		Mixed Amphetamine Salts N = 5570		Lisdexamfetamine N = 1272	
Clinical Outcome	% of Total Cases	Clinical Outcome	% of Total Cases	Clinical Outcome	% of Total Cases	Clinical Outcome	% of Total Cases
Tachycardia	52.9%	Tachycardia	55.7%	Tachycardia	57.4%	Tachycardia	59.7%
Agitation	29.4%	Agitation	43.8%	Agitation	39.4%	Agitation	35.1%
Chest pain (including noncardiac)	23.5%	Other - Miscellaneous	18.4%	Hypertension	24.9%	Hypertension	26.8%
Other - Miscellaneous	23.5%	Hypertension	17.8%	Other - Miscellaneous	22.2%	Other - Miscellaneous	23.3%
Vomiting	23.5%	Dizziness/vertigo	7.6%	Chest pain (including noncardiac)	9.1%	Hallucinations/delusions	9.0%
Hypertension	11.8%	Hallucinations/delusions	7.6%	Hallucinations/delusions	7.8%	Nausea	8.4%
Abdominal Pain	5.9%	Confusion	7.0%	Tremor	7.5%	Tremor	8.4%
Anorexia	5.9%	Drowsiness/lethargy	7.0%	Nausea	6.9%	Mydriasis	7.7%
Confusion	5.9%	Mydriasis	7.0%	Mydriasis	6.1%	Chest pain (including noncardiac)	7.5%
Diaphoresis	5.9%	Tremor	6.5%	Dizziness/vertigo	5.7%	Vomiting	6.5%
Methylphenidate N = 3123		Dexmethylphenidate N = 332		Methamphetamine (Prescription only) N = 31			
Clinical Outcome	% of Total Cases	Clinical Outcome	% of Total Cases	Clinical Outcome	% of Total Cases		
Tachycardia	58.3%	Tachycardia	59.6%	Tachycardia	51.6%		
Agitation	36.0%	Agitation	29.5%	Agitation	48.4%		
Hypertension	19.7%	Other - Miscellaneous	24.1%	Hypertension	29.0%		
Other - Miscellaneous	19.2%	Hypertension	20.8%	Other - Miscellaneous	22.6%		
Tremor	7.7%	Dizziness/vertigo	7.5%	Confusion	12.9%		
Nausea	6.2%	Mydriasis	7.2%	Drowsiness/lethargy	12.9%		
Drowsiness/lethargy	6.0%	Nausea	7.2%	Chest pain (including noncardiac)	9.7%		
Mydriasis	5.9%	Chest pain (including noncardiac)	6.0%	Fever/hyperthermia	9.7%		
Chest pain (including noncardiac)	5.5%	Hallucinations/delusions	5.7%	Hallucinations/delusions	9.7%		
Hallucinations/delusions	5.1%	Tremor	5.7%	Mydriasis	9.7%		

API, active pharmaceutical ingredient; NMU, nonmedical use; NOS, not otherwise specified.

Note: Schedule II stimulants only.

Note: Reports of regulated pharmaceutical and illicit cocaine exposures are considered together and are therefore excluded.

Note: Amphetamine exposures not referencing a specific prescription or illicit product are considered "Amphetamine (NOS)," and are also excluded.

Note: NMU consists of "Intentional – Misuse" and "Intentional – Abuse" exposures.

Note: Includes single-substance, related clinical outcome, prescription stimulant exposure cases only.

Note: Excludes prescription stimulant exposure cases with "Intentional - Suspected Suicide" and "Intentional - Unknown" reasons.

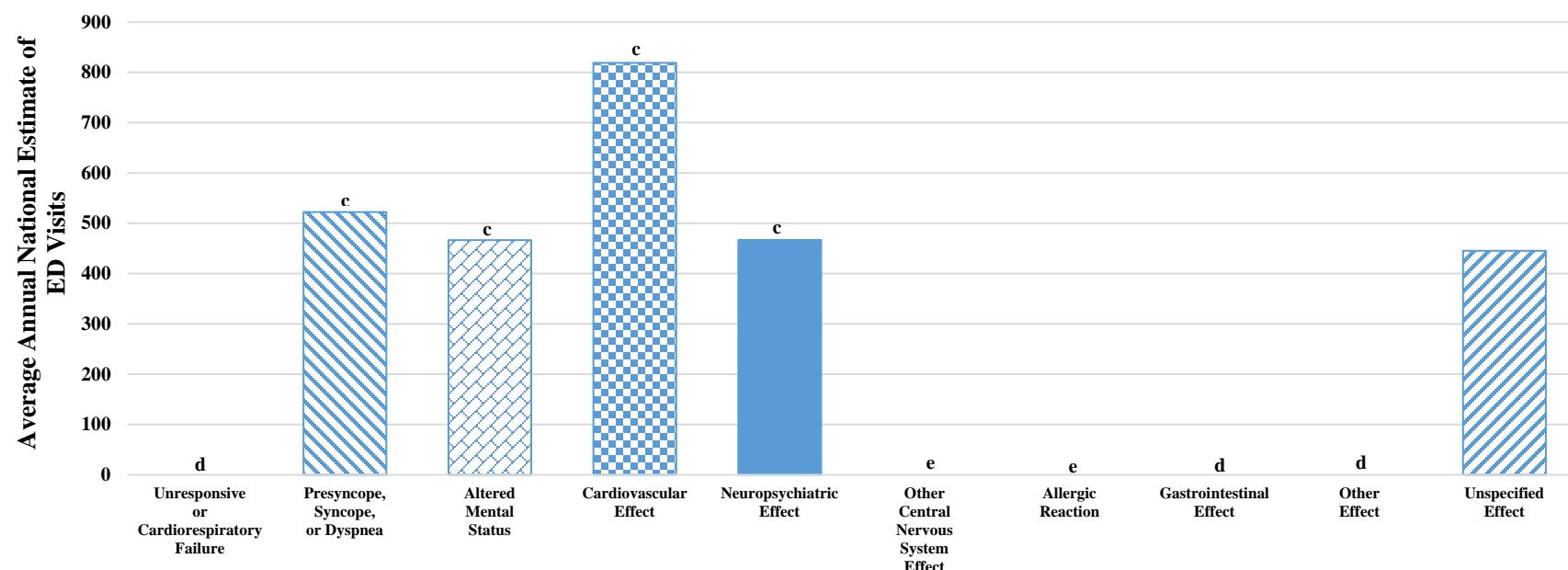
Note: Includes the ten most common single-substance, related clinical outcome prescription stimulant exposure cases.

Note: Children 5 years and younger are not included.

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

U.S. ED visits due to AEs involving NMU of prescription stimulants, captured in NEISS-CADES, are another source that can provide data on harms associated with NMU of prescription stimulants. From 2016 through 2018, there were an estimated 3,015 annual ED visits for harms from NMU of prescription stimulants alone (i.e., without any other documented substances). When stratified by clinical manifestation, an estimated 819 annual ED visits (CV=39%) involving NMU of prescription stimulants alone had one or more cardiovascular effects related to the prescription stimulant exposure, while presyncope, syncope, or dyspnea, altered mental status, and neuropsychiatric effects were each documented in over an estimated 400 annual ED visits involving NMU of prescription stimulants (CV=31% to 38%) (**Figure 63**). Cardiovascular effects were also some of the most commonly documented clinical manifestations/outcomes related to NMU of prescription stimulants in NPDS cases, as shown in **Table 46, above**.

Figure 63. National estimates of emergency department visits due to adverse events involving NMU^a of prescription stimulants alone, by clinical manifestation,^b 2016 to 2018



CV, coefficient of variation; ED, emergency department; NEISS-CADES, National Electronic Injury Surveillance System – Cooperative Adverse Drug Event Surveillance; NMU, nonmedical use.

Note: 'a' includes abuse, therapeutic misuse, and overdoses without documentation of therapeutic intent, self-harm, abuse, or misuse.

Note: 'b' Clinical manifestations were categorized in a mutually exclusive and hierarchical manner based on severity (e.g., a case involving shortness of breath and blurred vision would be classified as presyncope/syncope/dyspnea based on documentation of shortness of breath).

Note: 'c' indicates the estimate has a coefficient of variation >30% (CV = 38%, 34%, 39%, and 31%, respectively) and may be statistically unstable.

Note: 'd' indicates estimates based on <20 cases or total estimates <1,200 for the three-year period 2016-2018 are considered statistically unstable and are not shown.

Note: 'e' indicates that there were zero documented cases with the clinical manifestation.

Source: FDA-generated figure. National Electronic Injury Surveillance System – Cooperative Adverse Drug Event Surveillance (NEISS-CADES) project, Centers for Disease Control and Prevention.

U.S. ED visits were also analyzed to provide annual estimates of the number of visits for harms related to NMU of prescription stimulants relative to visits for harms related to NMU of prescription opioid analgesics. In 2016, approximately 11,000 U.S. ED visits (around 3% of total visits related to NMU of pharmaceuticals) were estimated to have involved NMU of stimulants with or without other substances,³⁷ whereas approximately 130,000 visits (around 36% of total visits related to NMU of pharmaceuticals) were estimated to have involved NMU of prescription opioid analgesics with or without other substances (**Table 48**).³⁸ When U.S. NMU ED visits in 2016 were restricted to single-substance only visits, an estimated 3,677 annual visits (1.0% of total visits related to NMU of pharmaceuticals) involved NMU of only stimulants, while an estimated 40,499 annual visits (11.3% of total visits related to NMU of pharmaceuticals) involved NMU of only prescription opioid analgesics.

Table 48. National estimates of ED visits due to NMU of pharmaceuticals, by category,^a 2016³⁸

Category	Implicated alone or with other substances, ^b annual national estimate ^d		Implicated alone without other substances, ^c annual national estimate ^e		
	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)
Nonopiod 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

^aEstimates 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 (—).

^bImplicated alone or in combination with other pharmaceuticals, alcohol, unspecified drugs, or illicit substances.

^cImplicated alone, without other categories of pharmaceuticals, and without alcohol, unspecified drugs, or illicit substances.

^dAnnual estimates and percentages total more than 100% because a single visit may involve multiple pharmaceuticals from different categories.

^eAnnual estimates and percentages total less than 100% because additional visits involve pharmaceuticals from different categories and additional visits involve alcohol or illicit substances.

^fCoefficient of variation >30%.

^gOther 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.

3.2.8.2 Pharmacovigilance Data

3.2.8.2.1 FAERS Case Series of Nonmedical CII Prescription Stimulant Use via a Non-Prescribed Route

In 2017, we retrieved 5,203 reports worldwide using the FAERS search strategy in **Table 6**. After we filtered using narrative text searches, applied the case definition in **Section 2.2.3.1**, and accounted for duplicate reports, we included 138 cases (42 U.S., 96 foreign) in the case series of nonmedical CII prescription stimulant use via a non-oral route. The top three reporter countries of the 96 foreign cases were France (n=37), Sweden (n=10), and Switzerland (n=10). A majority of the 96 foreign cases that

³⁷ Note: “Stimulants” were defined more broadly in the 2016 manuscript and may have also included over-the-counter (OTC) products like caffeine pills; however, prescription stimulants were likely implicated in the majority of visits.

³⁸ Geller AI, Dowell D, Lovegrove MC, McAninch JK, Goring SK, Rose KO, Weidle NJ, and Budnitz DS. U.S. Emergency Department Visits Resulting From Nonmedical Use of Pharmaceuticals, 2016. *Am J Prev Med*. 2019; 56 (5): 639-647. Table 2. ED Visits Due to Nonmedical Use of Pharmaceuticals, by Category, 2016. Page 643.

reported an age were in the age group of 25-44 years old (n=53). The U.S. cases were split almost evenly between the age group of 18-24 years old (n=9) and 25-44 years old (n=8) from 2007 through 2016.

In 2020, we conducted an updated FAERS search (**Table 6**) with the most recent Medical Dictionary for Regulatory Activities (MedDRA) terminology to retrieve 4,168 U.S. reports. After we filtered using narrative text searches, applied the case definition in **Section 2.2.3.1**, and accounted for duplicate reports, we included 50 U.S. cases in the case series of nonmedical CII prescription stimulant use via a non-oral route. A majority of these cases that reported an age were in the age group of 25-44 years old (n=24), followed by 18-24 years old (n=7), ≥45 years old (n=3), and one 17-year-old.

Table 49 and Table 50 show the descriptive case and event characteristics of the FAERS cases in the case series of nonmedical CII prescription stimulant use via non-oral route from 2007 to 2020. **Section 4.5** lists all the FAERS case numbers, FAERS version numbers, and Manufacturer Control numbers for these 188 cases.

Table 49. Descriptive case characteristics of FAERS cases of nonmedical CII prescription stimulant use via non-oral route, received by FDA from January 1, 2007 through April 23, 2020

	U.S. 2017-2020 (n=50)	U.S. 2007-2016 (n=42)	Foreign 2007-2016 (n=96)
Sex	(n=49)	(n=33)	(n=93)
Male	27	20	68
Female	22	13	25
Age, years	(n=35)	(n=24)	(n=72)
Mean	32	26	35
Median	31	23	34
Range	17-53	8-58	15-61
Report type			
Expedited (15-Day)	42	35	94
Non-Expedited	8	6	2
Direct	0	1	0
Serious outcomes*	(n=47)	(n=37)	(n=94)
Death	23	8	8
Hospitalization	20	11	41
Life-threatening	1	1	2
Disability	0	2	1
Other serious	22	20	67

CII, Schedule II; FAERS, FDA Adverse Event Reporting System; FDA, Food and Drug Administration; U.S., United States.
Note: '*' For the purposes of this review, the following outcomes qualify as serious: death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, required intervention and other serious important medical events. A case may have one or more outcome.
Source: FDA analysis of the Food and Drug Administration Adverse Event Reporting System., Time period from January 1, 2007 to December 31, 2016 searched on March 15, 2017, and time period from January 1, 2017 to April 24, 2020 searched on April 24, 2020.

Table 50. Descriptive event characteristics of FAERS cases of nonmedical CII prescription stimulant use via non-oral route, received by FDA from January 1, 2007 through April 23, 2020

	U.S. 2017-2020 (n=50)	U.S. 2007-2016 (n=42)	Foreign 2007-2016 (n=96)
Category of stimulant			
Methamphetamine	28*	3	2*
Amphetamine	13*	0	0
Mixed amphetamine salts	7*	11	1*
Methylphenidate	5	20†	94
Lisdexamfetamine	1	6	0
Dextroamphetamine	1	0	0
Dexmethylphenidate	0	2	0
Route of nonmedical stimulant use‡			
Snort	10	28	23
Inhalation	26	6	1
Injection/Parenteral	17	8	70
Insufflation	1	0	0
Chew (oral)	0	2	1
Cook (unspecified/oral)	0	1	1
Nonmedical use of stimulant only			
Yes	10	23	72
No	40	19	24
Concomitant substances abused or misused§	(n=40)	(n=19)	(n=24)
Opioid	28	6	12
Illicit drug	21	5	8
Cannabis	11	3	9
Benzodiazepine	7	1	6
Alcohol	6	3	4
Antihistamine	2	0	0
Modafinil	1	1	0
Acetaminophen	1	0	0
Antidepressant	1	0	0
Barbiturate	1	0	0
Dextromethorphan	1	0	0
Antipsychotic	0	1	1
Metoprolol	0	1	0
Ketamine	0	0	1
Zopiclone	0	0	1
Other	3	2	2
Prescription for stimulant			
Yes	5	12	32
No	1	6	21
Unknown	44	24	43
Reported reason for stimulant use	(n=5)	(n=12)	(n=32)
Attention-deficit/hyperactivity disorder	2	6	13
Narcolepsy	0	0	2
Other	0	1	6
Unknown	3	5	11

CII, Schedule II; FAERS, FDA Adverse Event Reporting System; FDA, Food and Drug Administration; U.S., United States.

Note: '*' indicates reported nonmedical use of more than one CII prescription stimulant. Four U.S. cases and one foreign case reported nonmedical use of amphetamine and methamphetamine. One U.S. case reported nonmedical use of mixed amphetamine salts and amphetamine.

Note: '†' Includes one case of methylphenidate transdermal system.

Note: '‡' indicates a case may report more than one route of nonmedical use. Non-oral routes of nonmedical use included injection, and inhalation by smoking or snorting. Nonmedical use by chewing (oral route) or cooking (unspecified route in one case and oral route in second case) were also reported.

Note: '§' indicates a case may report more than one substance of nonmedical use. Opioids reported included morphine, oxycodone, methadone, buprenorphine, and others. Illicit drugs reported included cocaine, heroin, methamphetamine, and others. Other included unspecified central nervous system depressant and unspecified substances.

Note: '||' Indicates the reason for stimulant use in "other" category included: treatment of cocaine withdrawal (n=1, foreign); weaning of illegal drug (n=1, foreign); disturbance in attention (n=1, foreign); depression (n=1, U.S.); mood disorder, not otherwise specified (n=1, foreign); psychomotor hyperactivity (n=1, foreign); and psychotic disorder (n=1, foreign).

Source: FDA analysis of the Food and Drug Administration Adverse Event Reporting System., Time period from January 1, 2007 to December 31, 2016 searched on March 15, 2017, and time period from January 1, 2017 to April 24, 2020 searched on April 24, 2020.

In the foreign FAERS case series from 2007 through 2016, the majority of the cases (98%) reported methylphenidate as the stimulant of NMU. The most commonly reported route of NMU was injection (73%), followed by snorting (24%). In the U.S. FAERS case series from 2007 to 2020, the largest number of the cases (34%) reported methamphetamine as the stimulant of NMU, with most cases not specifying if the methamphetamine was of prescription or illicit origin, and 58% of methamphetamine cases reporting concomitant illicit drug use. The most commonly reported route of NMU in the U.S. case series from 2007 to 2020 was snorting (41%), followed by inhalation that includes smoking and inhalation not further defined (35%).

We identified 71 U.S. cases of nonmedical CII prescription stimulant use via a non-oral route from 2007 to 2020 that reported one or more AEs which are categorized by System Organ Classes (SOCs) in **Table 51**.

Table 51. Adverse events by SOC reported in U.S. FAERS cases of nonmedical CII prescription stimulant use via non-oral route, received by FDA from January 1, 2007 through April 23, 2020 (sorted by decreasing number of total FAERS cases per SOC)

Row	Adverse Events by System Organ Class*	U.S. 2007-2020 (n=71)
1	Psychiatric disorders	49
2	Injury, poisoning and procedural complications	34
3	General disorders and administration site conditions	15
4	Respiratory, thoracic and mediastinal disorders	14
5	Nervous system disorders	13
6	Cardiac disorders	11
7	Vascular disorders	7
8	Gastrointestinal disorders	6
9	Musculoskeletal and connective tissue disorders	6
10	Investigations	5
11	Skin and subcutaneous tissue disorders	5
12	Hepatobiliary disorders	4
13	Infections and infestations	4
14	Social circumstances	4
15	Surgical and medical procedures	3
16	Blood and lymphatic system disorders	2
17	Eye disorders	2
18	Immune system disorders	1

Row	Adverse Events by System Organ Class*	U.S. 2007-2020 (n=71)
19	Metabolism and nutrition disorders	1
20	Product issues	1
21	Renal and urinary disorders	1

CII, Schedule II; FAERS, FDA Adverse Event Reporting System; FDA, Food and Drug Administration; SOC, System Organ Class; U.S., United States.
Note: '*' indicates a case may report more than one adverse event, and therefore a case may be categorized in more than one System Organ Class.
Source: FDA analysis of the Food and Drug Administration Adverse Event Reporting System., Time period from January 1, 2007 to December 31, 2016 searched on March 15, 2017, and time period from January 1, 2017 to April 24, 2020 searched on April 24, 2020.

Although 67 out of the 71 cases reported one or more serious outcomes, the most frequently reported AEs in the top SOCs were labeled events or events associated with drug dependence. Regarding the top five SOCs for the AEs most frequently reported with nonmedical CII prescription stimulant use, the AEs in the SOC *Psychiatric disorders* are predominantly labeled events for CII prescription stimulants (e.g., anxiety, euphoric mood, and paranoia) or are related to drug dependence (e.g., drug abuse, substance abuse, and drug withdrawal syndrome). As is expected, within the SOC *Injury, poisoning and procedural complications*, reported events were predominantly related to drug dependence (e.g., incorrect route of product administration, intentional product misuse, and toxicity to various agents). The most frequent AEs within the SOC *General disorders and administration site conditions* are either labeled events for CII prescription stimulants (e.g., chest pain) or are related to drug dependence (e.g., drug withdrawal syndrome). The AEs in the SOC *Respiratory, thoracic and mediastinal disorders* are predominantly labeled events for CII prescription stimulants (e.g., chest pain and dyspnoea). The most frequent AEs within the SOC *Nervous system disorders* are either labeled events for CII prescription stimulants (e.g., insomnia) or are related to drug overdose (e.g., loss of consciousness).

We provide example case summaries below, organized by route of NMU then by product, with significant AEs underlined.

Chew

- **Methylphenidate transdermal system**
 - A 19-year-old male, with a history of substance abuse, was prescribed methylphenidate transdermal system for ADHD. The patient stole 15 methylphenidate patches from a locked box and chewed the methylphenidate patches for euphoria (it was unknown how many patches were chewed). As a result, the patient experienced drug withdrawal.
- **Mixed amphetamine salts**
 - A 29-year-old female misused her prescribed mixed amphetamine salts by chewing the tablets. The patient chewed the tablets to “get more from the medication,” because she experienced a decreased effectiveness of the prescribed amphetamine after years of use. She reported that the tablets tasted like “flowers” (reported as product quality issue).

Cook

- **Dexmethylphenidate**
 - A physician reported that an 8-year-old male experienced an accidental overdose with dexmethylphenidate when the child ate 15 cookies that his mother prepared with one dexmethylphenidate extended-release 15 mg dose in each cookie. He was hospitalized with restlessness and tachycardia. He was treated and discharged from the hospital the following day.

Insufflation

- **Methylphenidate**
 - Wolf et al., 2016 reported an 18-year-old female who insufflated 110 mg of methylphenidate, “drank two capfuls of Molly’s Mosquito cap” (4-fluoroamphetamine, an illicit drug), and ingested 800 mg of prescription modafinil. The patient presented to the emergency department with headache, nausea, vomiting, weakness, and diaphoresis. Methylphenidate was undetectable in the urine drug screen (positive for amphetamines) and the gas chromatography-mass spectrometry drug screen (positive for amphetamines and modafinil). Therefore, the patient was diagnosed with acute dilated cardiomyopathy secondary to 4-fluoroamphetamine and modafinil.³⁹

Snorting

- **Methylphenidate**
 - A 15-year-old male with a history of fetal [alcohol] syndrome, ADHD, and bipolar disorder experienced chest pains after snorting the contents of a methylphenidate 10 mg capsule (prescribed for ADHD). He was admitted to the hospital with irregular heart rate, hypertension, and a blood clot in his leg, and subsequently a decreased respiratory rate. The patient’s concomitant medications included oxcarbazepine and quetiapine.
 - A patient of an unknown age reported a history of snorting methylphenidate for an unspecified duration. The patient reported that he experienced an irregular heart rate and chest pain when he overdosed on methylphenidate about ten years prior to the report.
- **Mixed amphetamine salts**
 - A 22-year-old male collapsed after snorting mixed amphetamine salts followed by binge alcohol drinking. The next morning, he was taken to the hospital after he was found unconscious on a sidewalk; he was brain dead and eventually taken off the ventilator.
 - Four cases reported multiple AEs consistent with the expected effects of the nasal abuse of medications or known adverse effects of mixed amphetamine salts. The AEs ranged from sinus-related issues and dyspnea (in a patient who also snorted alprazolam), weight decreased, abdominal discomfort, muscle twitching, to psychiatric-related AEs, such as hallucinations, paranoia, mood swings, agitation, and insomnia.
- **Lisdexamfetamine**
 - A male consumer snorted a friend’s prescribed lisdexamfetamine 50 mg; on unknown dates, he experienced epistaxis, vomiting, unable to speak, and “cognitive dulling.”
 - A female consumer snorted and ingested an unknown amount of lisdexamfetamine 70 mg capsules. The patient “passed out and was not breathing.” She was treated at the hospital and subsequently discharged the following day.

Injection

- **Methylphenidate**
 - Bolea-Alamanac et al., 2013 reported a *fatal outcome* in a 25-year-old pregnant female who abused methylphenidate and pentazocine (opioid) intravenously.⁴⁰ After delivery via an

³⁹ Wolf CE, Poklis JL, Cumpston K, Moss M, and Poklis A. Acute dilated cardiomyopathy and myocardial injury after combined 4-fluoroamphetamine and modafinil ingestion. *Drug Testing and Analysis*. 2016; 9 (4): 657-659. doi:10.1002/dta.1988

⁴⁰ Bolea-Alamanac BM, Green A, Verma G, Maxwell P, and Davies SJ. Methylphenidate use in pregnancy and lactation: a systematic review of evidence. *British Journal of Clinical Pharmacology*. 2013; 77 (1): 96-101. doi:10.1111/bcp.12138

- emergency Cesarean-section, the mother died secondary to pulmonary hypertension. The autopsy showed pulmonary granulomas.
- Three cases reported pulmonary talcosis, including two cases which also reported talc retinopathy.^{41,42,43} Note that two of the three cases also reported the abuse of concomitant medications intravenously.
 - Petzel and Eppert, 2010 reported a 29-year-old male who developed rhabdomyolysis, chest pain, and shortness of breath following the intravenous injection of 35 crushed methylphenidate 20 mg tablets suspended in water.⁴⁴
 - Stroup et al., 2010 reported a 24-year-old female who developed endocarditis following the abuse of methylphenidate and oxycodone intravenously, as well as marijuana use.⁴⁵ The patient was treated with six weeks of intravenous daptomycin in the hospital.
 - **Mixed amphetamine salts**
 - A 44-year-old male was taking buprenorphine and naloxone tablets for opioid type dependence. Following the recent intake of illicit methamphetamine and injection of **mixed amphetamine salts**, he was admitted to the hospital for abdominal pain and rectal bleeding. The patient was sedated for combativeness and admitted to the intensive care unit for mechanical ventilation. Additionally, he experienced withdrawal symptoms. At the time of the report, the patient was still in the hospital.

3.2.8.2.2 High-Level Overview of Nonmedical CII Stimulants Use Via the Oral Route

To provide context for the case series of nonmedical CII prescription stimulant use via a non-oral route, we present a high-level overview of the 5,680 U.S. FAERS reports of nonmedical CII prescription stimulant use via the oral route from January 1, 2007 through April 23, 2020. We use the terms “NMU” and “oral route” loosely in this high-level overview, because we did not review the narratives of all reports to confirm the reported event was related to the nonmedical CII prescription stimulant product use via the oral route. Additionally, these are total counts of FAERS reports and a hands-on analysis of the reports has not been performed. Therefore, report counts in this section may include duplicate reports, miscoded reports, or reports with insufficient information for assessment. Furthermore, reports may be unrelated to nonmedical CII prescription stimulant use due to various factors. We performed a FAERS search using the *Drug abuse and dependence (Standardized MedDRA Query (SMQ))* broad search, which included preferred terms (PTs) that may not be related to NMU, such as *Disturbance in social behaviour* or *Accidental overdose*. Additionally, reports could also be related to the NMU of an illicit stimulant, the NMU of a co-suspect medication, or other concomitant medications, instead of a CII prescription stimulant.

As depicted in **Table 52**, 72% of the reports reported at least one serious outcome, including death, which was reported for 50% of all reports.

⁴¹ Bastawrous S, and Hirschmann JV. A Man in His Early 70s With Progressive Dyspnea and Abnormal Fundoscopic Examination. *Chest*. 2014; 145 (1): 178-181. doi:10.1378/chest.13-1277

⁴² Mbuvah F, Venur VA, and Kistangari G. The Clinical Picture: An intravenous drug user with persistent dyspnea and lung infiltrates. *Cleveland Clinic Journal of Medicine*. 2014; 81 (4): 223-224. doi:10.3949/ccjm.81a.13082

⁴³ Schoenberger SD, and Agarwal A. Talc Retinopathy. *New England Journal of Medicine*. 2013; 368 (9): 852-852. doi:10.1056/nejmicm1203394

⁴⁴ Petzel R, and Eppert H. Methylphenidate Toxicity from Intravenous Injection of Oral Tablets. *Clinical Toxicology*. 2010; 48 (6): 604-667. doi: 10.3109/15563650.2010.493290

⁴⁵ Stroup JS, Wagner J, and Badzinski T. Use of Daptomycin in a Pregnant Patient with *Staphylococcus aureus* Endocarditis. *Annals of Pharmacotherapy*. 2010; 44 (4): 746-749. doi:10.1345/aph.1m650

Table 52. U.S. FAERS report count of nonmedical CII prescription stimulant use via the oral route by report type and serious outcomes, received by FDA from January 1, 2007 through April 23, 2020 (n=5,680)

Report Type		Seriousness			Reported Serious Outcomes*						
Direct	Expedited	Non-Expedited	Non-Serious	Serious	DE	HO	LT	DS	CA	RI	OT
109	3,662	1,909	1,585	4,095	2,859	730	134	35	0	10	1,544

CII, Schedule II; FAERS, FDA Adverse Event Reporting System; FDA, Food and Drug Administration; U.S., United States.
Note: '*' For the purposes of this review, the following outcomes qualify as serious: DE=Death, LT=Life-Threatening, HO=Hospitalization (initial or prolonged), DS=Disability, CA=Congenital Anomaly, RI=Required Intervention, and OT=Other serious important medical events. Each report may report more than one outcome. Reported outcomes are the coded serious outcomes submitted to FDA; causality and the role of the product in the coded outcome have not been determined for this evaluation.
Source: FDA analysis of the Food and Drug Administration Adverse Event Reporting System., Time period from January 1, 2007 to December 31, 2016 searched on March 15, 2017, and time period from January 1, 2017 to April 24, 2020 searched on April 24, 2020.

Of the reports with an age reported, the majority of reports was for the age group 17 to <65 years old (**Table 53**). We sampled the reports for the age group <3 years old, which generally reported intrauterine exposure, accidental exposure, disturbance in social behavior, tachycardia, or toxicity to various agents.

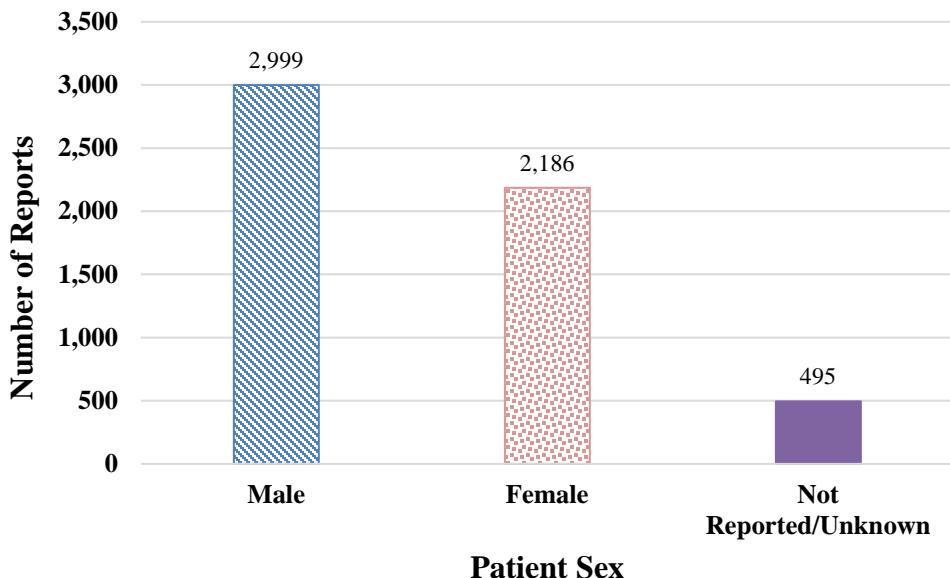
Table 53. U.S. FAERS report count of nonmedical CII prescription stimulant use via the oral route by age group and serious outcomes, received by FDA from January 1, 2007 through April 23, 2020 (n=5,680)

Age Group	Total Reports	Seriousness		Reported Serious Outcomes*						
		Non-Serious	Serious	DE	HO	LT	DS	CA	RI	OT
<1 year	9	1	8	4	2	0	0	0	0	3
1 - <3 years	14	2	12	7	6	0	0	0	0	5
3 - <7 years	116	95	21	2	6	0	1	0	0	14
7 - <17 years	606	379	227	70	75	19	6	0	2	124
17 - <65 years	3,403	292	3,111	2,534	500	96	22	0	8	929
>=65 years	84	14	70	60	11	1	1	0	0	15
NOT REPORTED	1,448	802	646	182	130	18	5	0	0	454
Total	5,680	1,585	4,095	2,859	730	134	35	0	10	1,544

CII, Schedule II; FAERS, FDA Adverse Event Reporting System; FDA, Food and Drug Administration; U.S., United States.
Note: '*' For the purposes of this review, the following outcomes qualify as serious: DE=Death, LT=Life-Threatening, HO=Hospitalization (initial or prolonged), DS=Disability, CA=Congenital Anomaly, RI=Required Intervention, and OT=Other serious important medical events. Each report may report more than one outcome. Reported outcomes are the coded serious outcomes submitted to FDA; causality and the role of the product in the coded outcome have not been determined for this evaluation.
Source: FDA analysis of the Food and Drug Administration Adverse Event Reporting System., Time period from January 1, 2007 to December 31, 2016 searched on March 15, 2017, and time period from January 1, 2017 to April 24, 2020 searched on April 24, 2020.

Of the reports with a patient sex reported, 58% were males compared to 42% females (**Figure 64**).

Figure 64. U.S. FAERS report count of nonmedical CII prescription stimulant use via the oral route by patient sex, received by FDA from January 1, 2007 through April 23, 2020 (n=5,680)



CII, Schedule II; FAERS, FDA Adverse Event Reporting System; FDA, Food and Drug Administration; U.S., United States.
Source: FDA analysis of the Food and Drug Administration Adverse Event Reporting System., Time period from January 1, 2007 to December 31, 2016 searched on March 15, 2017, and time period from January 1, 2017 to April 24, 2020 searched on April 24, 2020.

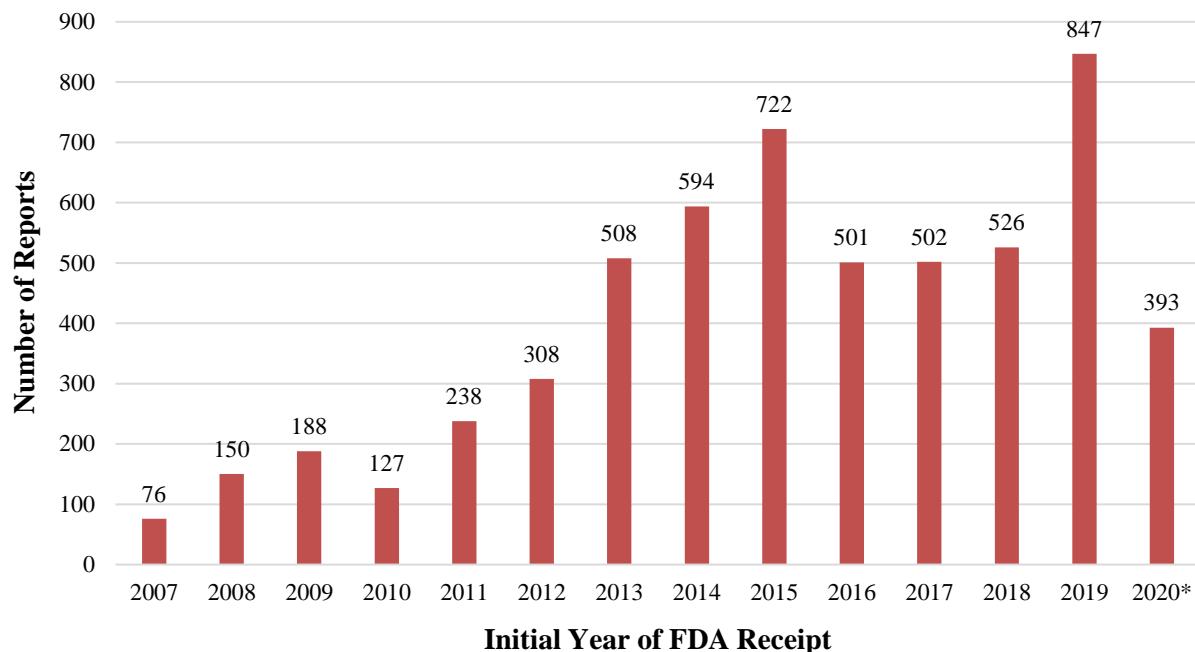
The number of U.S. FAERS reports received by the FDA spiked in 2015 and 2019 (Figure 65). The FDA's electronic reporting rule in 2015 may explain the spike in 2015. FDA's final rule on postmarketing safety report in electronic format, or known as the electronic reporting rule, was issued in June 2014 and became effective one year later.⁴⁶ Prior to the implementation of the electronic reporting rule, FDA received paper submissions of non-expedited reports when the periodic safety reports quarterly or annually. Furthermore, paper reports were not readily retrievable in FAERS.

Approximately 69% of the 2019 reports received by FDA were from AAPCC or referenced the AAPCC NPDS annual report, compared to about 22% in 2018. A vast majority of these reports received in 2019 referenced the 2017 Annual Report of the AAPCC NPDS published in 2018. In this report, Grummin et al. evaluated "substances of abuse and all closed human single substance exposures" from July 2010 through July 2018 by Generic Codes including both prescription and illicit substances (e.g., methamphetamine);⁴⁷ therefore, unless specified in the report narrative, it is not possible to determine the type of methamphetamine in the AAPCC reports in FAERS. Notably, about 79% of the AAPCC reports received in 2019 involved methamphetamine.

⁴⁶ FDA Issues Final Rule on Postmarketing Safety Report in Electronic Format. Available at: <https://www.fda.gov/medical-devices/postmarket-requirements-devices/mandatory-reporting-requirements-manufacturers-importers-and-device-user-facilities#:~:text=The%20FDA%20published%20a%20final,14%2C%202015>. (accessed June 19, 2020).

⁴⁷ Gummin DD, Mowry JB, Spyker DA, Brooks DE, Osterthaler KM, Banner W. 2017 Annual Report of the American Association of Poison Control Centers' National Poison Data System (NPDS): 35th Annual Report. *Clinical Toxicology*. 2018; 56 (12): 1213-1415.

Figure 65. U.S. FAERS report count of nonmedical CII prescription stimulant use via the oral route by initial FDA received year from January 1, 2007 through April 23, 2020 (n=5,680)



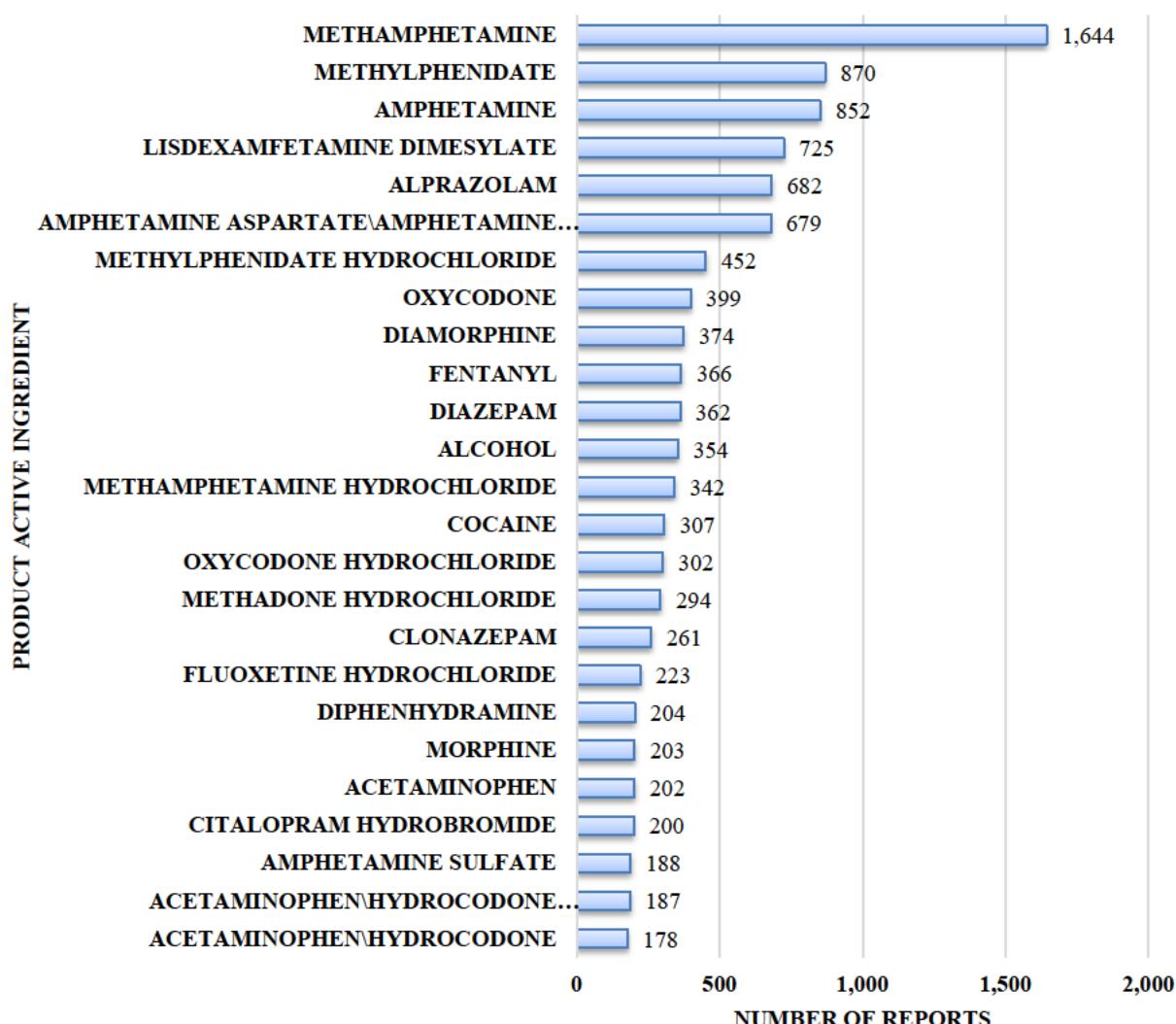
CII, Schedule II; FAERS, FDA Adverse Event Reporting System; FDA, Food and Drug Administration; U.S., United States.

Note: '*' indicates that 2020 is a partial year.

Source: FDA analysis of the Food and Drug Administration Adverse Event Reporting System., Time period from January 1, 2007 to December 31, 2016 searched on March 15, 2017, and time period from January 1, 2017 to April 24, 2020 searched on April 24, 2020.

As depicted in **Figure 66**, methamphetamine accounts for at least 29% of the products reported for all reports of nonmedical CII prescription stimulant use via the oral route (n=5,680). The number of reports involving methamphetamine in 2019 alone account for almost one-third of all methamphetamine reports from 2007 to 2020. Following methamphetamine, the top ten products include methylphenidate, amphetamine, lisdexamfetamine, benzodiazepine (alprazolam), mixed amphetamine salts, and opioids (oxycodone, diamorphine, fentanyl). Of note, in FAERS, CII prescription amphetamine products are more likely to be reported as mixed amphetamine salts (e.g. amphetamine aspartate / amphetamine sulfate / dextroamphetamine saccharate / dextroamphetamine sulfate); therefore, the reports of amphetamine alone are likely illicit products. Furthermore, it is difficult to determine from FAERS reports if the methamphetamine is a CII prescription product or an illicit product as stated above; however, based on the low utilization of CII prescription methamphetamine products in the U.S., most of the reports of methamphetamine likely involve illicit products. See **Figure 3** for prescription dispensed data in U.S. outpatient retail pharmacies for the CII prescription stimulants, including amphetamine alone and methamphetamine products.

Figure 66. U.S. FAERS report count of nonmedical CII prescription stimulant use via oral route by top twenty-five product active ingredients, received by FDA from January 1, 2007 through April 23, 2020* (n=5,680)

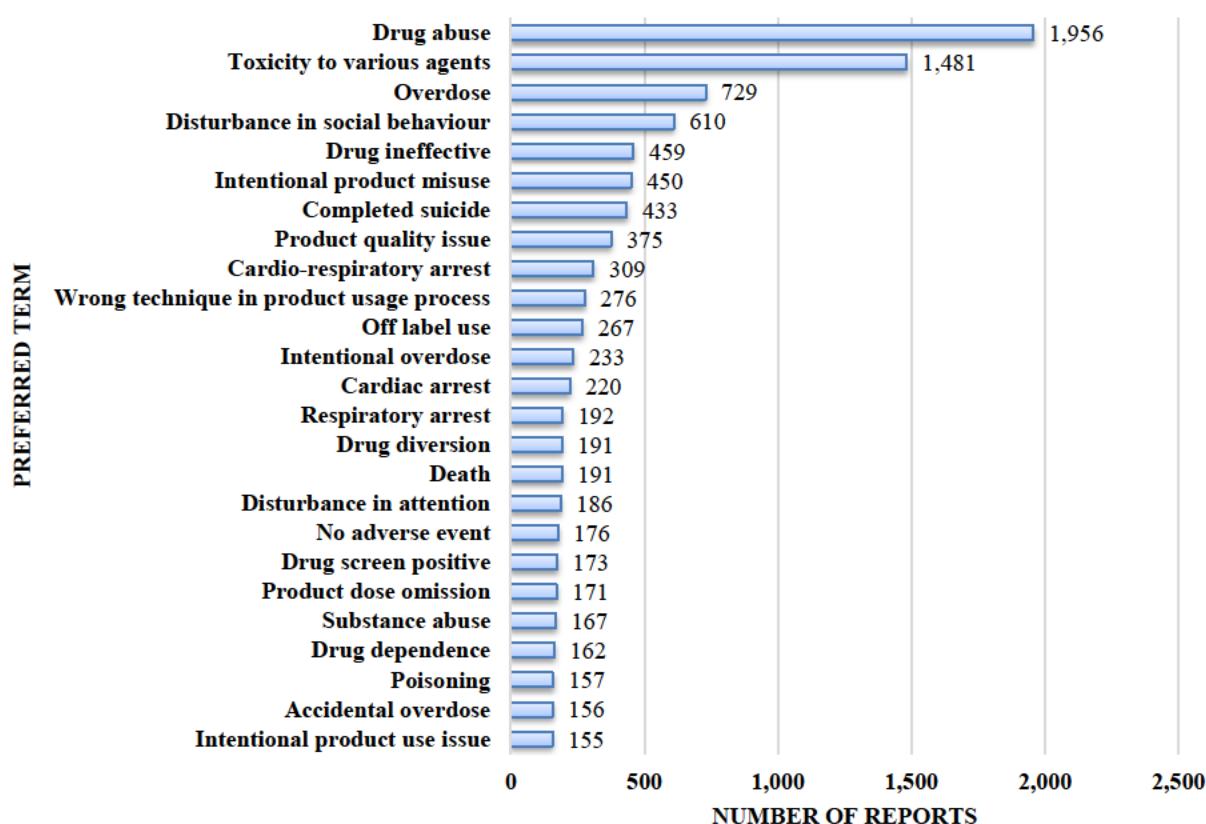


CII, Schedule II; FAERS, FDA Adverse Event Reporting System; FDA, Food and Drug Administration; U.S., United States.

Note: '*' This is a partial display of the total reports generated. The number of reports displayed on the graph may not add up to 5,680. Products are listed by the reported product active ingredient instead of the active moiety; therefore, a drug with a salt form may be listed twice (e.g. methylphenidate, methylphenidate hydrochloride). Each report may also contain more than one product or list the same product more than one time. Therefore, it is difficult to provide an estimate of the number of reports for each product or make comparisons between drug products. Source: FDA analysis of the Food and Drug Administration Adverse Event Reporting System. Time period from January 1, 2007 to December 31, 2016 searched on March 15, 2017, and time period from January 1, 2017 to April 24, 2020 searched on April 24, 2020

Half of the top ten PTs are likely related to, or consequences of, NMU (e.g., *Drug abuse, Toxicity to various agents, Overdose, Intentional product misuse, and Wrong technique in product usage process*) (**Figure 67**). In this patient population, FAERS reports coded with the PT *Disturbance in social behaviour* may be related to the indication of ADHD, rather than reports of NMU. FAERS reports coded with the PT *Death* usually provide little information on events that occurred prior to the death, or the cause of death. See **Figure 72** found in **Section 3.2.9.2.1** for the top PT list for fatal reports.

Figure 67. U.S. FAERS report count of nonmedical CII prescription stimulant use via the oral route by top twenty-five preferred terms, received by FDA from January 1, 2007 through April 23, 2020* (n=5,680)



CII, Schedule II; FAERS, FDA Adverse Event Reporting System; FDA, Food and Drug Administration; U.S., United States.

Note: * This is a partial display of the total reports generated. The number of reports displayed on the graph may not add up to 5,680. Each report may contain more than one Preferred Term.

Source: FDA analysis of the Food and Drug Administration Adverse Event Reporting System., Time period from January 1, 2007 to December 31, 2016 searched on March 15, 2017, and time period from January 1, 2017 to April 24, 2020 searched on April 24, 2020.

3.2.8.2.3 Medical Literature Regarding Morbidity Associated with Medical and Nonmedical CII Prescription Stimulants Use

We retrieved 246 articles relevant to medical and psychiatric complications of nonmedical CII prescription stimulant use with the search strategy described in **Table 7**. This section will include a discussion of articles regarding the wide range of adverse reactions related to medical and nonmedical CII prescription stimulants use administered orally, injected intravenously, or inhaled nasally, or through smoking. However, it is important to note that many of the articles did not or could not differentiate between morbidity from prescription and illicit CII stimulant (i.e., methamphetamine and cocaine) NMU.

These compounds are readily absorbed from the gastrointestinal tract, nasal mucosa, or deep lung, and they freely penetrate the blood-brain barrier.⁴⁸ Exposure results in marked norepinephrine and dopamine

⁴⁸ Albertson TE, Walby WF, and Derlet RW. Stimulant-induced pulmonary toxicity. *Chest*. 1995; 108 (4): 1140-9.

release and reuptake blockade, as well as moderate serotonin release and reuptake blockade.^{49,50} In addition, CII prescription stimulants can cause inhibition of monoamine oxidase, further increasing local concentrations of catecholamines. The mechanism of toxicity from exposure to CII prescription stimulants is primarily related to inhibition of norepinephrine and dopamine reuptake, which results in excessive extracellular dopamine and norepinephrine concentration. With excessive exposure, these pharmacologic effects lead to alpha-adrenoreceptor and beta-adrenoreceptor-mediated sympathomimetic syndrome.

People who use stimulants nonmedically describe feeling high and having a sense of increased power and self-confidence, as well as increased alertness and focus, improved concentration, and increased energy.⁵¹ They often also report feeling less depressed and anxious, having less need for sleep and rest, as well as appetite suppression. Administration of stimulants has considerable rewarding and reinforcing effects related to these experiences, further increasing the risk of chronic and excessive use (Volkow, 2003).⁵² Increased extracellular dopamine in the brain primarily underlies the reinforcing and therapeutic effects. People who nonmedically use these compounds can develop physical and psychological dependence, as well as addictive behaviors, including risky drug-seeking behaviors, and obsessive and compulsive preoccupation with obtaining the substances; these reactions can lead to impairment of important family, social, and occupational functioning. People who nonmedically use stimulants chronically can develop symptoms and signs of physiologic withdrawal, including lethargy, somnolence, irritability, and depression.

With acute or chronic use, especially at high doses, people who use stimulants can develop a wide range of neurologic, psychiatric, and behavioral abnormalities.^{53,54,55,56} Toxicities include psychotic symptoms such as paranoia, delusions, hallucinations (auditory, visual, and tactile), thought disorder, and grossly disorganized behavior. Delirium can occur, characterized by altered levels of consciousness, perceptual abnormalities, disturbance of attention and memory, disorientation, confusion, as well as psychomotor hyperactivity, mania, agitation, hyperkinesis, and aggressive behavior. Other neuropsychiatric reactions include severe anxiety, panic symptoms, insomnia, and sleep deprivation. Excessive neuromotor activation can cause seizures and movement disorders (dystonia, chorea, tremor, dysarthria, etc.). Excessive exposure increases the risks for violent behavior, unintentional and intentional self-injurious behavior, and possibly suicidal behavior. Some patients may require hospitalization, physical restraint, and medications to control severe neuropsychiatric complications. Such medications include antipsychotics, benzodiazepines, beta-blockers, and treatments for hyperthermia.

⁴⁹ Albertson TE, Walby WF, and Derlet RW. Stimulant-induced pulmonary toxicity. *Chest*. 1995; 108 (4): 1140-9.

⁵⁰ Spiller HA, Hays HL, and Aleguas A Jr. Overdose of drugs for attention-deficit hyperactivity disorder: clinical presentation, mechanisms of toxicity, and management. *CNS Drugs*. 2013; 27 (7): 531-543. doi: 10.1007/s40263-013-0084-8

⁵¹ Romach MK, Schoedel KA, and Sellers EM. Human abuse liability evaluation of CNS stimulant drugs. *Neuropharmacology*. 2014; 87: 81-90.

⁵² Volkow ND, and Swanson JM. Variables that affect the clinical use and abuse of methylphenidate in the treatment of ADHD. *Am J Psychiatry*. 2003; 160 (11): 1909-1918. doi: 10.1176/appi.ajp.160.11.1909

⁵³ Bruggisser M, Bodmer M, and Liechti ME. Severe toxicity due to injected but not oral or nasal abuse of methylphenidate tablets. *Swiss Med Wkly*. 2011; 141: w13267. doi: 10.4414/smw.2011.13267

⁵⁴ Pereiro-Gomez C, Vicente-Alba J, Ramos-Caneda A, Vazquez-Ventoso C, Fontela-Vivanco E, and Diaz del Valle JC. Ekbom syndrome in an intravenous methylphenidate abuse. *Adicciones*. 2012; 24 (4): 301-7.

⁵⁵ Verite F and Micallef J. Acute psychiatric symptoms during methylphenidate intravenous injections: A case report. *Therapie*. 2017; 72 (3):367-372. doi:10.1016/j.therap.2016.10.002

⁵⁶ Sanchez-Ramos J. Neurologic Complications of Psychomotor Stimulant Abuse. *Int Rev Neurobiol*. 2015; 120: 131-60.

Other important behavioral effects of excessive exposure to CII prescription stimulants include impulsivity, disinhibition, and impaired insight and judgment; all of these factors pose increased risks of numerous medical complications, such as trauma, infection, and other complications of intravenous injection, as well as legal and financial problems, and profound social and occupational dysfunction.⁵⁷ Neuropsychiatric toxicity and faulty insight and judgment can impair an individual's recognition of these problems and the need for treatment and rehabilitation. Haley et al. reported that nonmedical CII prescription stimulant use poses increased risks of risky driving behavior, aggression, motor vehicle accidents, and death.⁵⁸ Nonmedical stimulant use is associated with violent behavior and penetrating traumatic injury.⁵⁹ In one study, 46% of trauma patients were positive for at least one drug of abuse, including CII prescription stimulants. Farrel et al. observed a 6-fold increase in mortality associated with CNS stimulant abuse (including prescription and illicit drugs), compared to the general population.⁶⁰ There were also increased rates of violence and injury, depression, suicide, psychosis, other psychiatric AEs, and homicide.

Numerous serious cardiovascular and cerebrovascular adverse reactions can occur related to excessive catecholamine concentrations and sympathetic activation from the release of norepinephrine, dopamine, and serotonin from neuronal terminals in the CNS and autonomic nervous system.⁶¹ Reactions include sudden cardiac death, myocardial infarction and other acute coronary syndromes, acute and chronic hypertension, cardiomyopathy, myocarditis, and atrial and ventricular arrhythmia.⁶² Amphetamine also inhibits the enzyme monoamine oxidase, which effectively increases catecholaminergic tone. Sympathetic activation leads to tachycardia, vasoconstriction, labile blood pressure, ischemic and hemorrhagic stroke, and atrial and ventricular arrhythmia.⁶² In addition, increased adrenergic tone can lead to cardiac hypertrophy and left ventricular dysfunction. Hypertension is common, but severe hypotension can also occur related to paradoxical sympathetic suppression, (which is a late complication of catecholamine depletion), or ventricular impairment induced by ischemia or mechanical complications. Various mechanisms can contribute to myocardial infarction. Diffuse or local coronary artery spasm can occur in normal and atherosclerotic arteries. Hemodynamic changes associated with sympathetic activation increase oxygen demand. Chronic use of stimulants can cause repetitive episodes of coronary spasm and paroxysms of hypertension, which can cause endothelial damage, coronary artery dissection, and acceleration of atherosclerosis.⁶² Necrotizing vasculitis of medium and small arteries can lead to widespread ischemia. Prolonged NMU can result in irreversible dilated cardiomyopathy secondary to ischemia and fibrosis, myocyte necrosis, and myocardial injury from exposure to infectious agents or toxins such as heavy metals. Noncardiogenic pulmonary edema and pulmonary hypertension can also occur.

Other mechanical cardiovascular complications from increased blood pressure include aortic dissection or cardiac valve trauma (mostly aortic and mitral valves), which increases the risk of endocarditis.⁶³ Endocarditis is often associated with unusual organisms such as *Candida*, *Pseudomonas*, or *Klebsiella*.

⁵⁷ London ED. Impulsivity, Stimulant Abuse, and Dopamine Receptor Signaling. *Adv Pharmacol*. 2016; 76: 67-84.

⁵⁸ Haley AC, Hart CL, O'Malley KY, Stough CKK, and Downey LA. Risky driving behaviours among stimulant drug users and the role of aggression: findings from a national survey. *Addiction*. 2019; 114 (12): 2187-2196.

⁵⁹ Armenian P, Effron Z, Garbi N, Dirks R, Benowitz NL, and Gerona RR. Stimulant drugs are associated with violent and penetrating trauma. *American Journal of American Medicine*. 2019; 37 (4): 645-650.

⁶⁰ Farrel M, Martin NK, Stockings E, Borquez A, Cepeda JA, Degenhardt L, Ali R, Tran LT, Torrens M, Shoptaw S, and McKetin R. Responding to global stimulant use: challenges and opportunities. *Lancet*. 2019; 394: 1652-1667.

⁶¹ Ghuran A and Nolan J. Recreational drug misuse issues for the cardiologist. *Heart*. 2000; 83 (6): 627-633.

⁶² Asaki Y and Ohishi M. Cerebrovascular and cardiovascular diseases caused by drugs of abuse. *Hypertension Research*. 2020; 43: 363-371.

⁶³ Bruggisser M, Bodmer M, and Liechti ME. Severe toxicity due to injected but not oral or nasal abuse of methylphenidate tablets. *Swiss Med Wkly*. 2011; 141: w13267. doi: 10.4414/smw.2011.13267

Infectious endocarditis frequently has an aggressive course, with severe valvular destruction, abscess formation, and a requirement for surgery. Excessive stimulant use can cause a wide range of supraventricular and potentially lethal ventricular arrhythmias. Sudden cardiovascular collapse can occur as a result of myocardial ischemia and infarction, arrhythmia, acute heart failure, or mechanical complications. Treatment of cardiotoxicity may be required, including mechanical cardiac and ventilator support, alpha-receptor and beta-receptor blockade, vasodilators, antiarrhythmics, oxygen, aspirin, and benzodiazepines. Angioplasty and thrombolytics may be necessary. Other cardiovascular and neurologic complications can include hemorrhagic cerebrovascular accidents and cerebral vasculitis.^{63,64}

Chronic nonmedical methamphetamine use (mainly via smoking) can cause cardiomyopathy with a unique histological pattern.⁶⁵ Excessive use can cause dyspnea, dilated cardiomegaly with left ventricular hypertrophy, as well as multiple infarcts without significant coronary artery disease. Death can occur, resulting from cardiac and liver disease, or urosepsis. Unique cardiomyocyte histologic features include generalized vacuolization, enlarged, bizarre shaped nuclei, generalized hypertrophy, and marked perivascular fibrosis and interstitial fibrosis.

There are numerous serious risks related to injection of amphetamine, methamphetamine, and methylphenidate products.⁶³ Toxicity can be related to the pharmacological effects of stimulants and excipients as well as infectious agents. Accidental intra-arterial injection can lead to vasoconstriction, vasospasm, endothelial damage, ischemia, thrombosis, embolism, and tissue necrosis (fingers and forearm) necessitating amputation. Infectious diseases associated with injection, needle sharing, and risky sexual behavior include HIV/AIDS, hepatitis B and C viral infection, bacteremia, endocarditis, sepsis, and abscess formation.^{66,67} Complications of intravenous injection can require surgical intervention and treatment with antiviral drugs and intravenous antibiotics. Exposure to excipients from crushed tablets or solvents can cause foreign body reactions and granulomatous disease (dermatologic, pulmonary, and vascular). Foreign body reactions can occur secondary to talcosis (magnesium and silicon toxicity), including talc retinopathy.^{68,69} Severe systemic effects from intravenous injection of CII prescription stimulants include hyperthermia, renal failure, rhabdomyolysis, placental abruption, low-birth weight, and disseminated vasculitis.^{70,71}

Albertson, et al. describes a wide range of pulmonary complications secondary to excessive exposure to inhalation (nasal and smoking) of CII prescription and illicit stimulants, excipients, and contaminants.⁷² Toxicities include complications of barotrauma (pneumothorax, pneumopericardium, and

⁶⁴ Miyashita T, Hayashi T, Ishida Y, Tsuneyama K, Kimura A, and Kondo T. A fatal case of pontine hemorrhage related to methamphetamine abuse. *J Forensic Leg Med.* 2014; 14 (7): 444-447.

⁶⁵ Karch SB. The Unique histology of methamphetamine cardiomyopathy: a case report. *Forensic Sci Int.* 2011; 212 (1-3): e1-e4. doi:10.1016/j.forsciint.2011.04.028

⁶⁶ Volkow ND and Swanson JM. Variables that affect the clinical use and abuse of methylphenidate in the treatment of ADHD. *Am J Psychiatry.* 2003; 160 (11): 1909-1918. doi: 10.1176/appi.ajp.160.11.1909

⁶⁷ Kall KI and Olin RG. HIV status and changes in risk behavior among intravenous drug users in Stockholm 1987-1988. *Aids.* 1990; 4 (2): 153-157.

⁶⁸ Tse DT and Ober RR. Talc Retinopathy. *Am J Ophthalmol.* 1980; 90 (5): 624-40.

⁶⁹ Nakano H, Iwata Y, Kanegae H, Oshima T, Aizawa H, and Hara N. Talc pulmonary granulomatosis caused by intravenous administration of methylphenidate. *Nihon Kokyuki Gakkai Zasshi.* 1998; 36 (1): 111-115.

⁷⁰ Bruggisser M, Bodmer M, and Liechti ME. Severe toxicity due to injected but not oral or nasal abuse of methylphenidate tablets. *Swiss Med Wkly.* 2011; 141: w13267. doi: 10.4414/smw.2011.13267

⁷¹ Spiller HA, Hays HL, and Aleguas A Jr. Overdose of drugs for attention-deficit hyperactivity disorder: clinical presentation, mechanisms of toxicity, and management. *CNS Drugs.* 2013; 27 (7): 531-543. doi: 10.1007/s40263-013-0084-8

⁷² Albertson TE, Walby WF, and Derlet RW. Stimulant-induced pulmonary toxicity. *Chest.* 1995; 108 (4):1140-1149. doi:10.1378/chest.108.4.1140

pneumomediastinum), pulmonary and alveolar hemorrhage and infarct, pulmonary edema, asthma exacerbation, eosinophilic lung disease, chronic interstitial pneumonia and fibrosis, pulmonary hypertension, respiratory depression, and nasal septal perforation. Other severe reactions include foreign body aspiration, aspiration pneumonia, bronchiolitis obliterans, granulomatous reactions, epiglottitis, bronchitis, emphysema, sinusitis, airway trauma and burns, and tracheal stenosis. Albertson, et al. acknowledges the limitations of some of the supportive studies and findings: incomplete controlling for the effects of concomitant use of tobacco, marijuana, cocaine, and other substances, as well as adulterants such as talc and cellulose.

People who use CII prescription stimulants nonmedically frequently use a wide range of other prescription products and illicit substances, including alcohol, marijuana, cocaine, methamphetamine, prescription opioids, heroin, benzodiazepines, and sedative-hypnotics. Some of the negative pharmacologic effects of stimulants may motivate people to self-treat with CNS depressants. Exposure to the above concomitantly used substances further increases the risk of medical and functional complications.

Bachi and colleagues discuss evidence suggesting that various types of substance abuse, dependence, and addiction can accelerate biological aging processes.⁷³ Substance use disorders are associated with early onset of age-related disease, secondary to drug-induced multi-system toxicity and perilous lifestyles, which are often undetected, unreported, and untreated. Pathophysiological processes that may hasten aging in relation to addiction include oxidative stress and cellular aging, inflammation in the periphery and CNS, decline in brain volume and function, and early onset of cardiac, cerebrovascular, kidney, and liver disease. Timely detection, prevention, and treatment of substance use complications and accelerated aging processes in addiction are crucial for the prevention of premature morbidity and mortality.

3.2.9 Mortality Associated with NMU of Prescription Stimulants

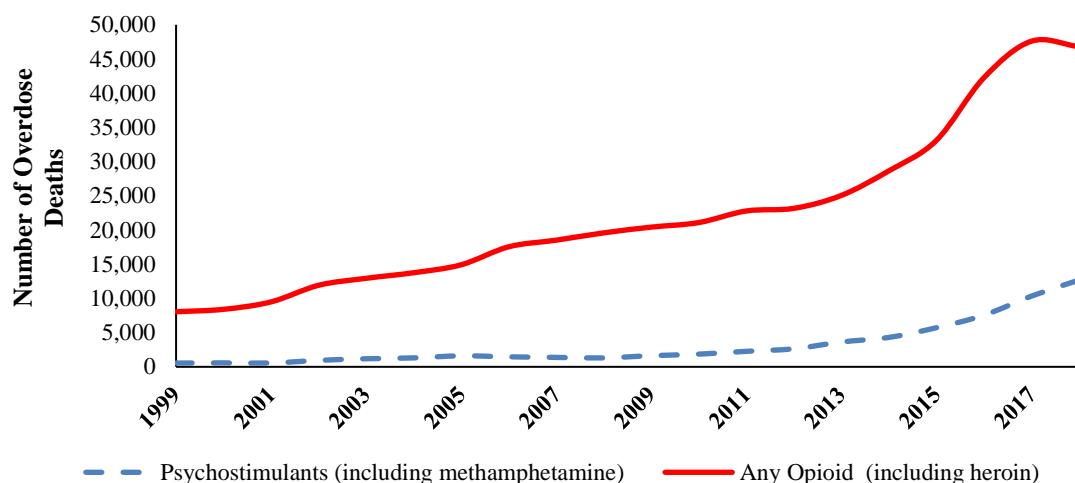
3.2.9.1 Epidemiology Data

3.2.9.1.1 National Vital Statistics System Multiple Cause of Death Data

Publicly available data on U.S. deaths involving CII prescription stimulants are limited by the fact that these products are grouped under the same ICD-10 code as other stimulants, including methamphetamine and other illicit stimulant drugs, such as Ecstasy (T43.6: psychostimulants with abuse potential). The category of all opioid overdose deaths also includes illicit opioids such as heroin and illicit fentanyl. Nonetheless, data from the CDC, presented in **Figure 68**, provide some high-level information on the relative number of overdose deaths involving stimulants versus opioids (including heroin), and the respective trends in overdose mortality for these drug classes. These data illustrate the now widely recognized increase in overdose deaths involving opioids, but also increasing annual numbers of deaths involving psychostimulant drugs, particularly since around 2011. However, as of 2018, the number of psychostimulant overdose deaths remained much lower than the number of opioid overdose deaths. These figures only include deaths for which the underlying cause was categorized as an overdose and would not include deaths from other causes (e.g., car accident, infectious complication, myocardial infarction) to which these drugs contributed.

⁷³ Bachi K, Sierra S, Volkow ND, Goldstein, and Alia-Klein N. Is biological aging accelerated in drug addiction? *Curr Opinion Behavioral Sciences*. 2016; 13: 34-39.

Figure 68. Annual number of overdose deaths in the U.S. involving psychostimulants and opioids, National Vital Statistics System Multiple Cause of Death Database, 1999 to 2018



U.S., United States.

Note: Drug overdose deaths are identified using *International Classification of Diseases, Tenth Revision* underlying cause-of-death codes X40–X44, X60–X64, X85, and Y10–Y14. Drug overdose deaths involving selected drug categories are identified by specific multiple-cause-of-death codes: “Opioids” include heroin (T40.1); natural and semisynthetic opioids (T40.2); methadone (T40.3); and synthetic opioids excluding methadone (T40.4); “Psychostimulants” refers to psychostimulants with abuse potential (T43.6). Psychostimulants with abuse potential include such drugs as methamphetamine, amphetamine, methylphenidate.

Source: FDA-generated figure. Data Brief 356. Drug Overdose Deaths in the United States, 1999–2018. Accessed from https://www.cdc.gov/nchs/data/databriefs/db356_tables-508.pdf#3.

3.2.9.1.2 National Data on Drug-Involved Mortality: Deaths with Stimulant Involvement

Because of the noted limitations related to limited differentiation of prescription stimulants from publicly available mortality data, the above analysis was supplemented with national data on stimulant-involved mortality using death certificate literal text, made available to the Agency by the National Center for Health Statistics.⁷⁴ Of note, published analyses indicate that the reporting of at least one specific drug in the death certificate literal text has improved during the study period,⁷⁵ so there may be some contribution to increasing trends over time from better reporting of specific drugs in death certificates.

Table 54 shows the number of deaths involving selected stimulants among U.S. residents, for years 2010 to 2014. Methamphetamine was involved in the largest number of deaths (19,268 decedents), followed by amphetamine (3,493 decedents), although it is unclear what proportion of amphetamine deaths specifically involved a CII prescription stimulant containing amphetamine salts and in what proportion refers to the general amphetamine class of drugs, including methamphetamine. The number of deaths increased for methamphetamine and amphetamine during the study period.

The other CII stimulants included in this analysis (i.e., methylphenidate, dextroamphetamine, dexamphetamine, lisdexamfetamine) were involved in a small minority of deaths (range: 2 to 142 deaths per stimulant, or 166 total deaths). Involvement of these four stimulants occurred among mutually exclusive deaths (e.g., dextroamphetamine was not involved in the same deaths as dexamphetamine). While there was an increase in deaths involving other stimulants from 2013 to 2014, the absolute number

⁷⁴ An updated analysis of these data was not possible at the time of this review as we were unable to access the National Center for Health Statistics’ Research Data Center due to restrictions associated with the ongoing SARS-CoV-2 pandemic.

⁷⁵ Warner M, Trinidad JP, Bastian BA, Miniño AM, and Hedegaard H. Drugs Most Frequently Involved in Drug Overdose Deaths: United States, 2010–2014. *Natl Vital Stat Rep.* 2016; 65 (10): 1-15.

of deaths was low in all years relative to the number of deaths for the methamphetamine and amphetamine categories.

Table 54. Number of deaths involving selected stimulants, among U.S. residents, 2010 to 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

U.S., United States.

Note: Deaths involving more than one drug (e.g., a death involving both methamphetamine and amphetamine) are counted in totals for each drug.
Source: NCHS, National Vital Statistics System, Mortality files linked with death certificate literal text, constructed for analysis on October 6, 2016.

Table 55 shows the overlap of different stimulants (i.e., methamphetamine, amphetamine, and other stimulants) involved in mortality of U.S. residents between 2010 and 2014. Overall, 96% of deaths were associated with a single stimulant. The majority of these were due to methamphetamine, which was involved in over 18,000 single stimulant deaths, representing 95% (18,395 out of 19,268 deaths) of all deaths with methamphetamine involvement. Among deaths involving amphetamine, 75% (2,609 out of 3,493 deaths) involved only amphetamine. A similar percentage of other stimulant involved deaths (75%, or 125 out of 166 deaths) involved only other stimulants (i.e., not methamphetamine or amphetamine).

Table 55. Combinations of stimulants involved in mortality, U.S. residents, 2010 to 2014

	Stimulant involvement in death			Number of Deaths n = 22,027
	Methamphetamine	Amphetamine	Other Stimulants*	
Single-stimulant involvement	Involved	Not involved	Not involved	18,395 (84%)
	Not involved	Involved	Not involved	2,609 (12%)
	Not involved	Not involved	Involved	125 (1%)
Multi-stimulant involvement	Not involved	Involved	Involved	25 (0%)
	Involved	Involved	Not involved	857 (4%)
	Involved	Not involved	Involved	14 (0%)
	Involved	Involved	Involved	2 (0%)

U.S., United States.

Note: ** Other stimulants includes methylphenidate, dextroamphetamine, dexmethylphenidate, and lisdexamfetamine.
Source: NCHS, National Vital Statistics System, Mortality files linked with death certificate literal text, constructed for analysis on October 6, 2016.

Table 56 shows the number of stimulant-involved deaths by selected characteristics. Across the three stimulant groups (methamphetamine, amphetamine, and other stimulants), approximately 90% of all stimulant-involved deaths occurred among middle-aged decedents (i.e., persons aged 25 to 64 years). Fewer deaths occurred among the younger age groups, including <1% of total deaths involving individuals aged 17 years or younger. The age-specific rates of stimulant-involved deaths also showed a similar pattern among the age groups (**Table 57**). There was a consistently higher number of stimulant-involved deaths among males than females. However, male deaths were more common than female deaths for methamphetamine-involved deaths (2.6 times) than for deaths involving amphetamine (1.7 times) or other stimulants (1.2 times).

In general, deaths are classified as either natural deaths (e.g., deaths caused by cardiac arrhythmia) or deaths due to external injuries. Among external injuries, there are unintentional, intentional, homicide, and undetermined manner of deaths. Poisoning (overdose) is a type of external injury. Across the

stimulant groups, a majority of deaths (range 61% to 66%) were classified as unintentional external injuries. Natural deaths involving methamphetamine (27%) and amphetamine (20%) were also common. For all three stimulant categories, a majority of deaths were classified as overdoses (range: 65% to 87%). Involvement of non-stimulant drugs, nicotine, and alcohol was lower for deaths involving methamphetamine (36%) than for amphetamine (68%) or other stimulants (80%).

Table 56. Number (%) of deaths involving selected stimulants, by decedent characteristic, U.S. residents, 2010 to 2014

Characteristic	Methamphetamine n = 19,268	Amphetamine n = 3,493	Other Stimulants* n = 166
Age group			
<5	93 (0%)	10 (0%)	0 (0%)
5-13	23 (0%)	7 (0%)	2 (1%)
14-17	51 (0%)	22 (1%)	9 (5%)
18-24	1,055 (5%)	336 (10%)	17 (10%)
25-44	7,871 (41%)	1,721 (49%)	68 (41%)
45-64	9,664 (50%)	1,318 (38%)	66 (40%)
>64	511 (3%)	79 (2%)	4 (2%)
Sex			
Female	5,378 (28%)	1,278 (37%)	74 (45%)
Male	13,890 (72%)	2,215 (63%)	92 (55%)
Manner of Death			
Natural	5,141 (27%)	687 (20%)	12 (7%)
Suicide	671 (3%)	278 (8%)	38 (23%)
Unintentional	12,690 (66%)	2,368 (68%)	102 (61%)
Other**	766 (4%)	160 (5%)	14 (8%)
Overdose			
Yes	12,447 (65%)	2,526 (72%)	145 (87%)
No	6,821 (35%)	967 (28%)	21 (13%)
Involves non-stimulant drugs, nicotine, and alcohol			
Yes	6,996 (36%)	2,384 (68%)	133 (80%)
No	12,272 (64%)	1,109 (32%)	33 (20%)

U.S., United States.

Note: Deaths involving more than one drug (e.g., a death involving both methamphetamine and amphetamine) are counted in totals for each drug.

Note: ** Other stimulants include methylphenidate, dextroamphetamine, dexmethylphenidate, and lisdexamfetamine.

Note: *** indicates that 'Other' manner of death includes homicide, legal, medical complications, and undetermined.

Source: NCHS, National Vital Statistics System, Mortality files linked with death certificate literal text, constructed for analysis on October 6, 2016.

Table 57. Annual rate of deaths involving selected stimulants per 1 million U.S residents, by age group, 2010 to 2014

Characteristic	Methamphetamine	Amphetamine	Other Stimulants*
Age group			
Not specified	Not applicable	Not applicable	Not applicable
<5	1.4	0.1	0.0
5-13	0.0	0.0	0.0
14-17	0.6	0.3	0.1
18-24	6.7	2.1	0.1
25-44	18.9	4.1	0.2
45-64	23.3	3.2	0.2
>64	2.3	0.4	0.0

U.S., United States.
 Notes: Deaths involving more than one drug (e.g., a death involving both methamphetamine and amphetamine) are incorporated in the rates for each drug.
 Note: * Other stimulants include methylphenidate, dextroamphetamine, dexmethylphenidate, and lisdexamfetamine.
 Sources: NCHS, National Vital Statistics System, Mortality files linked with death certificate literal text, constructed for analysis on October 6, 2016. Bridged-race vintage 2015 (2010-2015) postcensal population estimates (US DHHS, 2017).

To help provide context for the above analysis, results from a previously published report by the National Vital Statistics System are provided in **Table 58**. This report describes the fifteen drugs most commonly involved in overdose deaths from 2011 to 2016. Other than methamphetamine (most likely illicit), amphetamine was the only other stimulant API in the top 15 drugs mentioned on overdose death certificates from 2011 to 2016 and was documented as being involved in 1.9% of overdose deaths, whereas opioid analgesic APIs (e.g., hydrocodone, oxycodone, morphine) were frequently in the top fifteen drugs. Overall, 2016 death certificate mentions show that fentanyl, heroin, and cocaine were the top three drugs involved in drug overdose deaths. It is important to note that these comparisons do not account for substantial differences in prescription volume for these products. As described previously in **Figure 8** found in **Section 3.1.5.** prescriptions for opioid analgesics, as a class, outnumber those for CII stimulants by a factor of approximately 2 to 1, although this ratio varied by year. Rather, these comparisons are intended to provide contextual information on the relative public health burden of mortality associated with these two classes of prescription drugs.

Table 58. Top fifteen drugs involved in drug overdose deaths: United States, 2011 to 2016⁷⁶

2011 (n = 41,340)			2012 (n = 41,502)			2013 (n = 43,982)			
Rank ¹	Referent drug	Number of deaths ²	Percent of deaths ³	Referent drug	Number of deaths ²	Percent of deaths ³	Referent drug	Number of deaths ²	Percent of deaths ³
1	Oxycodone.....	5,587	13.5	Heroin	6,155	14.8	Heroin	8,418	19.1
2	Cocaine	5,070	12.3	Oxycodone.....	5,178	12.5	Cocaine	5,319	12.1
3	Heroin	4,571	11.1	Cocaine	4,780	11.5	Oxycodone	4,967	11.3
4	Methadone	4,545	11.0	Methadone.....	4,087	9.8	Morphine	3,772	8.6
5	Alprazolam	4,066	9.8	Alprazolam.....	3,803	9.2	Alprazolam	3,724	8.5
6	Morphine	3,290	8.0	Morphine	3,513	8.5	Methadone	3,700	8.4
7	Hydrocodone	3,206	7.8	Hydrocodone	3,037	7.3	Methamphetamine	3,194	7.3
8	Methamphetamine	1,887	4.6	Methamphetamine	2,267	5.5	Hydrocodone	3,113	7.1
9	Diazepam	1,698	4.1	Fentanyl	1,615	3.9	Fentanyl	1,919	4.4
10	Fentanyl	1,662	4.0	Diazepam	1,577	3.8	Diazepam	1,618	3.7
11	Diphenhydramine	1,226	3.0	Diphenhydramine	1,300	3.1	Diphenhydramine	1,360	3.1
12	Oxymorphone	1,190	2.9	Citalopram	1,042	2.5	Tramadol	1,009	2.3
13	Citalopram	1,043	2.5	Tramadol	935	2.3	Clonazepam	946	2.2
14	Acetaminophen	879	2.1	Oxymorphone	866	2.1	Citalopram	914	2.1
15	Tramadol	849	2.1	Amitriptyline.....	835	2.0	Amitriptyline.....	815	1.9
2014 (n = 47,055)									
2014 (n = 47,055)			2015 (n = 52,404)			2016 (n = 63,632)			
Rank ¹	Referent drug	Number of deaths ²	Percent of deaths ³	Referent drug	Number of deaths ²	Percent of deaths ³	Referent drug	Number of deaths ²	Percent of deaths ³
1	Heroin	10,882	23.1	Heroin	13,318	25.4	Fentanyl	18,335	28.8
2	Cocaine	5,892	12.5	Fentanyl	8,251	15.7	Heroin	15,961	25.1
3	Oxycodone	5,431	11.5	Cocaine	7,324	14.0	Cocaine	11,316	17.8
4	Alprazolam	4,237	9.0	Oxycodone	5,792	11.1	Methamphetamine	6,762	10.6
5	Fentanyl	4,223	9.0	Methamphetamine	5,092	9.7	Alprazolam	6,209	9.8
6	Morphine	4,024	8.6	Alprazolam	4,801	9.2	Oxycodone	6,199	9.7
7	Methamphetamine	3,747	8.0	Morphine	4,226	8.1	Morphine	5,014	7.9
8	Methadone	3,498	7.4	Methadone	3,376	6.4	Methadone	3,493	5.5
9	Hydrocodone	3,299	7.0	Hydrocodone	3,051	5.8	Hydrocodone	3,199	5.0
10	Diazepam	1,748	3.7	Diphenhydramine	1,798	3.4	Diazepam	2,022	3.2
11	Diphenhydramine	1,614	3.4	Diazepam	1,796	3.4	Diphenhydramine	2,008	3.2
12	Tramadol	1,175	2.5	Clonazepam	1,328	2.5	Clonazepam	1,656	2.6
13	Clonazepam	1,139	2.4	Gabapentin	1,222	2.3	Gabapentin	1,546	2.4
14	Citalopram	1,014	2.2	Tramadol	1,177	2.2	Tramadol	1,250	2.0
15	Oxymorphone	909	1.9	Oxymorphone	1,006	1.9	Amphetamine	1,193	1.9

¹Ranks were not tested for statistical significance.²Number of drug overdose deaths involving the referent drug.³Percentage of drug overdose deaths involving the referent drug.NOTES: Drug overdose deaths are identified using *International Classification of Diseases, Tenth Revision* (ICD-10) underlying cause-of-death codes X40–X44, X60–X64, X85, and Y10–Y14. Deaths may involve other drugs in addition to the referent drug (i.e., the one listed). Deaths involving more than one drug (e.g., a death involving both heroin and cocaine) are counted in both totals. Caution should be used when comparing numbers across years. The reporting of at least one specific drug or drug class in the literal text, as identified using ICD-10 multiple cause-of-death codes T36–T50.8, improved from 75% of drug overdose deaths in 2011 to 85% of drug overdose deaths in 2016.

SOURCE: NCHS, National Vital Statistics System, Mortality files linked with death certificate literal text, 2011–2016.

3.2.9.2 Pharmacovigilance Data

3.2.9.2.1 Fatal FAERS Reports

Non-Oral Route

We included 31 fatal U.S. cases that reported abuse or misuse of CII prescription stimulants via non-prescribed routes from January 1, 2007 through April 23, 2020. The age range of the cases was 17 to 46 years old, and the mean age was 29 years (n=29). Eight of the cases were female, 22 males, and the sex was not reported in one case.

The 31 U.S. cases with a fatal outcome reported nonmedical CII prescription stimulant use by: inhalation (n=20; smoking=1), intranasal (n=4), injection (n=3), parenteral (n=1), or multiple routes (n=3; inhalation, injection, or oral). NMU of stimulants were: methamphetamine (n=16), amphetamine (n=12), mixed amphetamine salts (n=5), or methylphenidate (n=2), with four cases reporting polysubstance nonmedical stimulant use. Although the methamphetamine cases were reported to a manufacturer of methamphetamine, it was often not clear that the individual in fact used a CII prescription stimulant product versus illicit methamphetamine. The reported reason for use was unknown for 28 fatal cases. In two cases, NMU with only a stimulant was reported (monotherapy methamphetamine abuse and monotherapy mixed amphetamine salts abuse); in 29 cases, there was polysubstance NMU involving one

⁷⁶ Hedegaard H, Bastian BA, Trinidad JP, Spencer M, and Warner M. Drugs Most Frequently Involved in Drug Overdose Deaths: United States, 2011–2016. *National Vital Statistics Reports*. 2018; 67 (9): 1-13.

or more prescription stimulants as well as one or more of the following: alcohol, antihypertensive, antipsychotic, cannabis, opioid, cocaine, heroin, antihistamine, benzodiazepine, antitussive, antidepressant, acetaminophen, or CNS depressant.

Most of the fatal cases were complex; these involved polysubstance NMU and patients with numerous medical or psychiatric comorbidities. These risk factors included: coronary artery disease, cardiac disorder, respiratory disease, infectious disease, renal disease, or psychiatric disorder including bipolar disorder, depression, and psychotic disorder. As a result, it was difficult to determine whether the deaths and other AEs were solely or directly attributable to the effects of the stimulant abused. The probable or possible causes of death were as follows: multi drug toxicity (n=17), serious cardiac event (n=7), respiratory arrest secondary to opioid toxicity (n=2), compartment syndrome (n=2), unknown (n=2), infectious endocarditis or bacteremia (n=1). In the reviewer's assessment, the pharmacologic effect of the stimulant probably contributed to the death in 26 cases and possibly contributed to the death in four cases. In the remaining case reporting endocarditis and bacteremia, the cause of death appeared to be primarily related to the intravenous injection route of administration.

Oral Route

The age and sex breakdown of the fatal U.S. FAERS reports are similar to those described in **Section 3.2.8.2.2** for all U.S. FAERS reports of nonmedical CII stimulants use via the oral route. Of the fatal reports with an age reported, the majority of reports were for the age group 17 to <65 years old (**Table 59**). We sampled the reports for the age group <3 years old, which generally reported intrauterine exposure, accidental exposure, disturbance in social behavior, tachycardia, or toxicity to various agents.

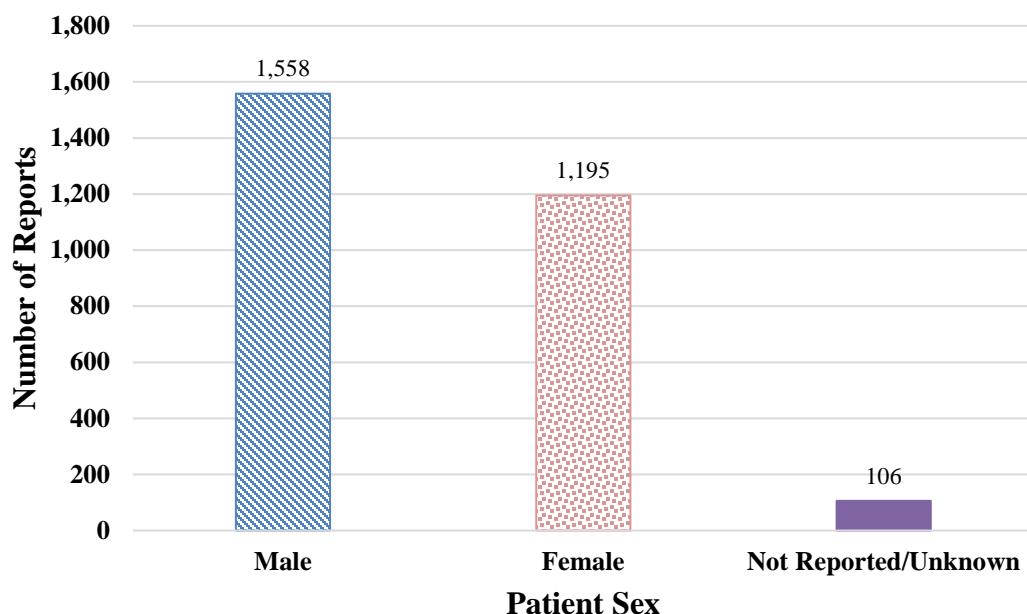
Table 59. Fatal U.S. FAERS report count of CII prescription stimulant NMU via the oral route by age group, received by FDA from January 1, 2007 through April 23, 2020 (n=2859)

Age Group	Total Cases	Reported Serious Outcomes*						
		DE	HO	LT	DS	CA	RI	OT
<1 year	4	4	0	0	0	0	0	0
1 - <3 years	7	7	3	0	0	0	0	1
3 - <7 years	2	2	0	0	0	0	0	1
7 - <17 years	70	70	7	1	0	0	1	12
17 - <65 years	2,534	2,534	220	43	0	0	1	484
≥65 years	60	60	7	0	0	0	0	8
NOT REPORTED	182	182	20	3	0	0	0	44
Total	2,859	2,859	257	47	0	0	2	550

CII, Schedule II; FAERS, FDA Adverse Event Reporting System; FDA, Food and Drug Administration; U.S., United States.
Note: '*' For the purposes of this review, the following outcomes qualify as serious: DE=Death, LT=Life-Threatening, HO=Hospitalization (initial or prolonged), DS=Disability, CA=Congenital Anomaly, RI=Required Intervention, and OT=Other serious important medical events. Each report may report more than one outcome. Reported outcomes are the coded serious outcomes submitted to FDA; causality and the role of the product in the coded outcome have not been determined for this evaluation.
Source: FDA analysis of the Food and Drug Administration Adverse Event Reporting System., Time period from January 1, 2007 to December 31, 2016 searched on March 15, 2017, and time period from January 1, 2017 to April 24, 2020 searched on April 24, 2020.

Of the reports with a patient sex reported, 57% were males compared to 43% females (**Figure 69**).

Figure 69. Fatal U.S. FAERS report count of CII prescription stimulant NMU via the oral route by patient sex, received by FDA from January 1, 2007 through April 23, 2020 (n=2859)



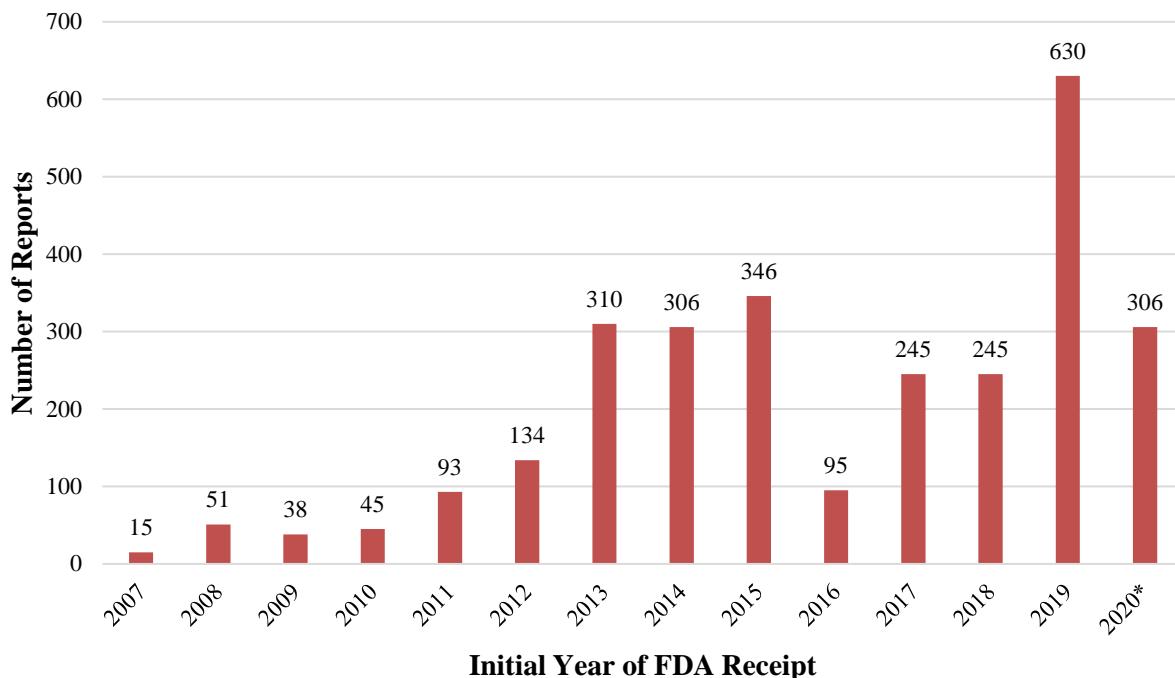
CII, Schedule II; FAERS, FDA Adverse Event Reporting System; FDA, Food and Drug Administration; U.S., United States.

Source: FDA analysis of the Food and Drug Administration Adverse Event Reporting System., Time period from January 1, 2007 to December 31, 2016 searched on March 15, 2017, and time period from January 1, 2017 to April 24, 2020 searched on April 24, 2020.

Figure 70 shows the number of fatal U.S. FAERS reports that reported CII prescription stimulant NMU via an oral route, by year, from January 1, 2007 to April 23, 2020. Approximately 92% of the 2019 fatal reports were reported by AAPCC or referenced the AAPCC NPDS annual report, compared to 47% in 2018. A vast majority of the AAPCC fatal reports received in 2019 referenced the 2017 AAPCC NPDS Annual Report published in 2018.⁷⁷

⁷⁷ Gummin DD, Mowry JB, Spyker DA, Brooks DE, Osterthaler KM, Banner W. 2017 Annual Report of the American Association of Poison Control Centers' National Poison Data System (NPDS): 35th Annual Report. *Clinical Toxicology*. 2018; 56 (12): 1213-1415.

Figure 70. Fatal U.S. FAERS report count of CII prescription stimulant NMU via the oral route by initial FDA received year from January 1, 2007 through April 23, 2020 (n=2859)



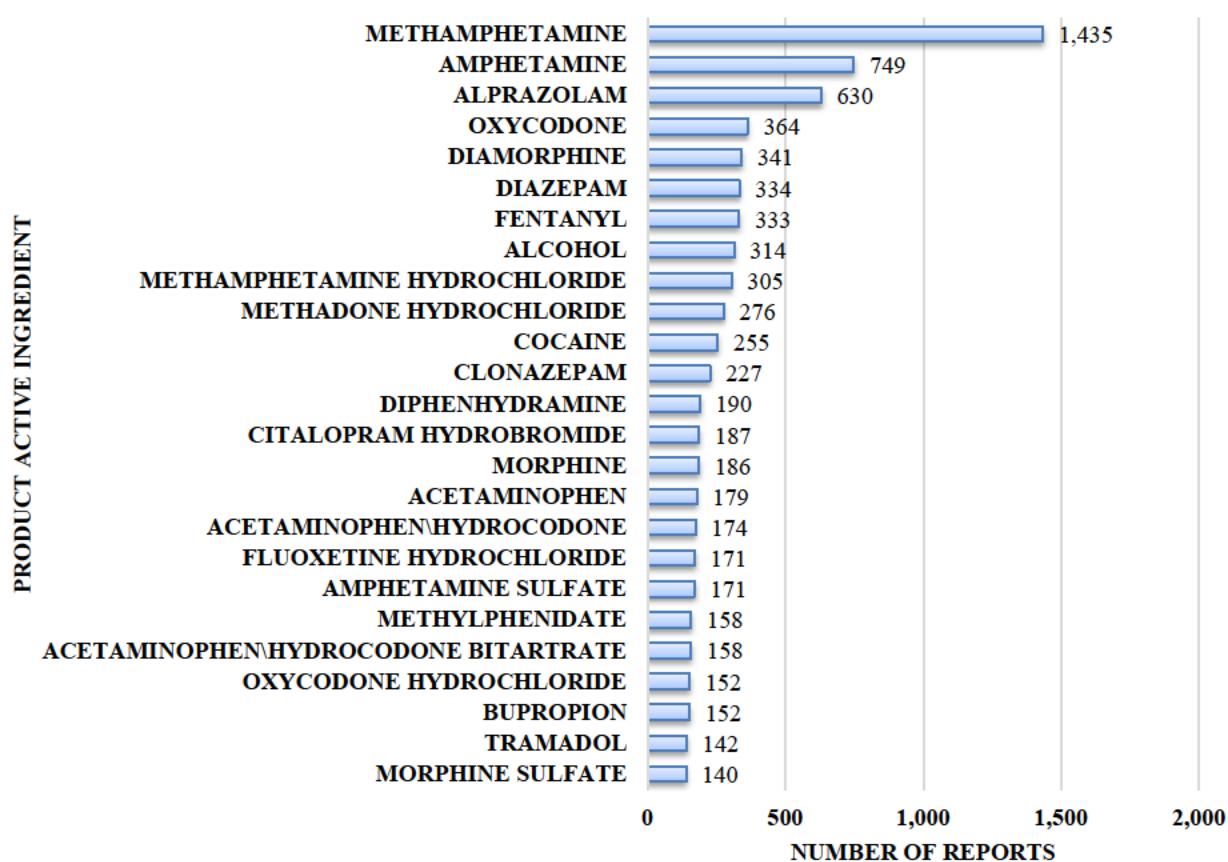
CII, Schedule II; FAERS, FDA Adverse Event Reporting System; FDA, Food and Drug Administration; U.S., United States.

Note: '*' indicates that 2020 is a partial year.

Source: FDA analysis of the Food and Drug Administration Adverse Event Reporting System., Time period from January 1, 2007 to December 31, 2016 searched on March 15, 2017, and time period from January 1, 2017 to April 24, 2020 searched on April 24, 2020.

As depicted in **Figure 71**, the top ten products listed in the fatal reports (n=2859) are methamphetamine, amphetamine, benzodiazepines (alprazolam, diazepam), opioids (oxycodone, diamorphine, fentanyl, methadone), and alcohol. Of note, 79% of the fatal reports from AAPCC in 2019 involved methamphetamine. As mentioned in **Section 3.2.8.2.2**, in FAERS, CII prescription amphetamine products are more likely to be reported as mixed amphetamine salts (e.g. amphetamine aspartate / amphetamine sulfate / dextroamphetamine saccharate / dextroamphetamine sulfate); therefore, the reports of amphetamine alone are likely illicit products. Furthermore, it is difficult to determine from FAERS reports if the methamphetamine is a CII prescription product or an illicit product; however, based on the low utilization of CII prescription methamphetamine products in the U.S., most of the reports of methamphetamine likely involve illicit products. See **Section 3.1.2** for sales distribution data for the CII prescription stimulants, including methamphetamine.

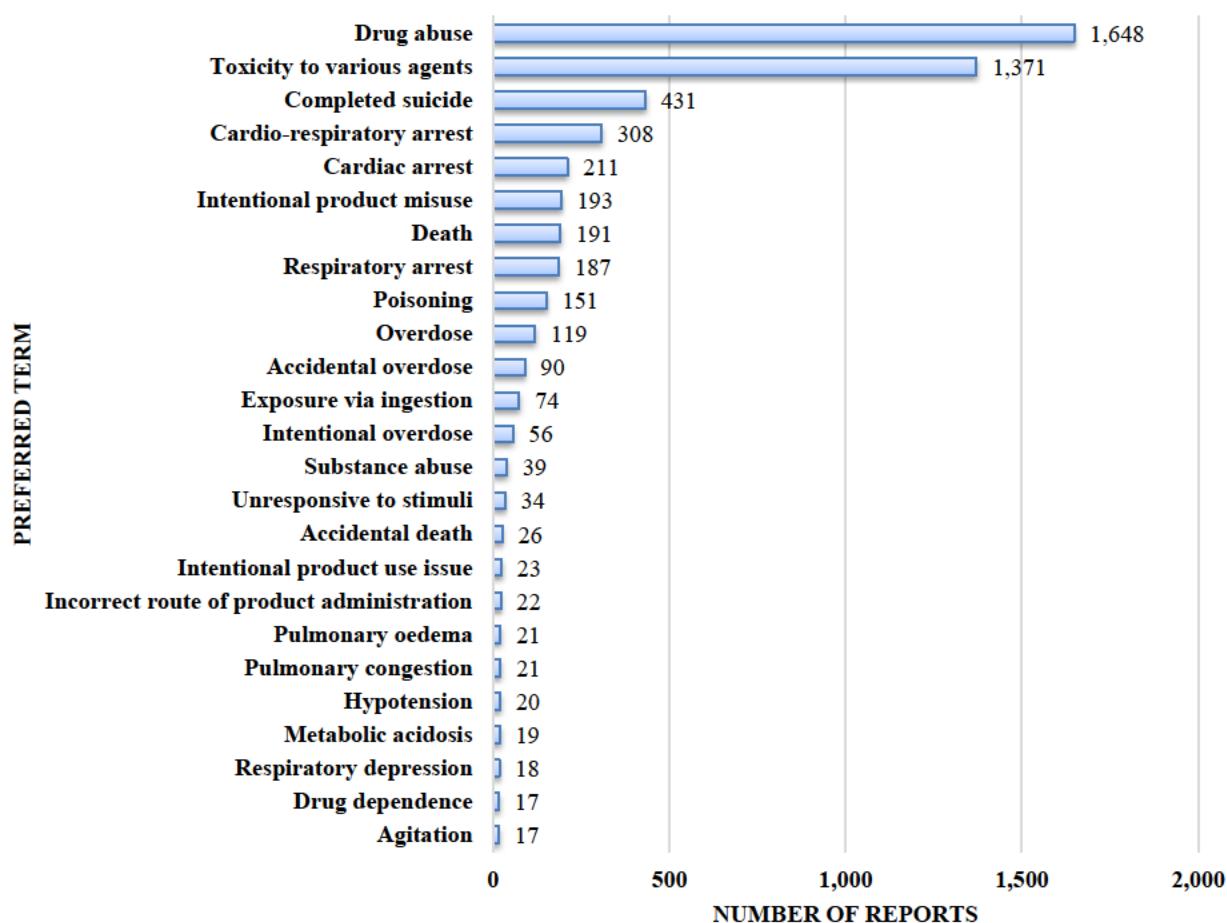
Figure 71. Fatal U.S. FAERS report count of CII prescription stimulant NMU via oral route by top twenty-five product active ingredients, received by FDA from January 1, 2007 through April 23, 2020* (n=2859)



CII, Schedule II; FAERS, FDA Adverse Event Reporting System; FDA, Food and Drug Administration; U.S., United States.

Note: '*' This is a partial display of the death reports generated. The number of cases displayed on the graph may not add up to 2859. Products are listed by the reported product active ingredient instead of the active moiety; therefore, a drug with a salt form may be listed twice (e.g., methamphetamine, methamphetamine hydrochloride). Each report may also contain more than one product or list the same product more than one time. Therefore, it is difficult to provide an estimate of the number of reports for each product or make comparisons between drug products. Source: FDA analysis of the Food and Drug Administration Adverse Event Reporting System., Time period from January 1, 2007 to December 31, 2016 searched on March 15, 2017, and time period from January 1, 2017 to April 24, 2020 searched on April 24, 2020.

Figure 72. Fatal U.S. FAERS report count of CII prescription stimulant NMU via the oral route by top twenty-five preferred terms, received by FDA from January 1, 2007 through April 23, 2020* (n=2859)



CII, Schedule II; FAERS, FDA Adverse Event Reporting System; FDA, Food and Drug Administration; U.S., United States.

Note: '*' This is a partial display of the total reports generated. The number of cases displayed on the graph may not add up to 2859. Each case may contain more than one Preferred Term.

Source: FDA analysis of the Food and Drug Administration Adverse Event Reporting System, Time period from January 1, 2007 to December 31, 2016 searched on March 15, 2017, and time period from January 1, 2017 to April 24, 2020 searched on April 24, 2020.

3.2.9.2.2 Medical Literature Regarding Mortality Associated with Medical and Nonmedical CII Prescription Stimulant Use

We did not retrieve additional fatal case reports or articles that specifically discussed mortality of nonmedical CII prescription stimulant use with the medical literature search described in **Table 7**. However, numerous adverse reactions discussed in **Section 3.2.8.2.3** are potentially life-threatening. This includes the following types of adverse reactions associated with CII prescription stimulant misuse and abuse: cardiovascular, cerebrovascular, psychiatric and behavioral, unintentional and intentional injury, penetrating trauma, motor vehicle accidents, infectious disease, and pulmonary reactions.

4 ADDITIONAL METHODOLOGY AND RESULTS

4.1 DRUG UTILIZATION DATABASE DESCRIPTIONS AND DATA TABLES

IQVIA, National Sales Perspectives™, Retail and Non-Retail

IQVIA, National Sales Perspectives™ measures the volume of drug products, both prescription and over-the-counter, and selected diagnostic products moving from manufacturers into various outlets within the retail and non-retail markets. Volume is expressed in terms of eaches and share of market. These data are based on national projections. Outlets within the retail market include the following pharmacy settings: chain drug stores, independent drug stores, mass merchandisers, food stores, and mail service. Outlets within the non-retail market include clinics, non-federal hospitals, federal facilities, HMOs, long-term care facilities, home health care, and other miscellaneous settings. Estimates provided in this review are national estimates, but statistical tests were not performed to determine whether statistically significant changes occurred over time or between products; therefore, all changes over time should be considered approximate. In addition, these results cannot be validated through medical chart reviews.

IQVIA National Prescription Audit™

The IQVIA National Prescription Audit™ measures the “retail outflow” of prescriptions, or the rate at which drugs move out of retail pharmacies, mail service houses, or long-term care facilities into the hands of consumers via formal prescriptions in the United State. The National Prescription Audit™ measures what is dispensed by the pharmacist. Data for the National Prescription Audit™ is a national level estimate of the drug activity from retail pharmacies. National Prescription Audit™ receives over 3.7 billion prescription claims per year, captured from a sample of the universe of approximately 59,900 pharmacies throughout the United States. The pharmacies in the database account for most retail pharmacies and represent nearly 93% of retail prescriptions dispensed nationwide. The type of pharmacies in the sample are a mix of independent, retail, chain, mass merchandisers, and food stores with pharmacies, and include prescriptions from cash, Medicaid, commercial third-party and Medicare Part-D prescriptions. Data is also collected from approximately 45 to 75% (varies by class and geography) of mail service pharmacies and approximately 71 to 83% of long-term care pharmacies. Data are available on-line for 72-rolling months with a lag of 1 month.

IQVIA Total Patient Tracker™

IQVIA Total Patient Tracker™ is a national-level projected service designed to estimate the total number of unique (non-duplicated) patients across all drugs and therapeutic classes in the retail outpatient setting from U.S. retail pharmacies. Data are available back to January 2002 and are available 20 days after the close of the month. IQVIA Total Patient Tracker™ uses prescription activity as part of its projection and integrates information from pharmacies and payers to eliminate duplicate patients and multiple prescription fills, producing quick and reliable unique patient counts. IQVIA has 92% coverage and a sample of ~58,900 retail pharmacies. IQVIA captures about 3.8 billion transactions annually. IQVIA Total Patient Tracker™ is projected to the known universe of retail pharmacies.

Of note, the estimated prescription and/or patient counts provided are based on projections of sample prescription claims data and therefore have some degree of inherent sampling error. These estimates are not intended to be representations of exact enumerations and should be interpreted with caution particularly if they are based on a small sample size. In addition, the data cannot be validated due to lack of access to medical records in the data sources.

Syneos Health Treatment Answers™

Syneos Health TreatmentAnswers™ and TreatmentAnswers™ with Pain Panel is a monthly survey designed to provide descriptive information on the patterns and treatment of diseases encountered in

office-based physician practices in the United States. The survey consists of data collected from over 3,200 office-based physicians representing 30 specialties across the United States that report on all patient activity during one typical workday per month. These data may include profiles and trends of diagnoses, patients, drug products mentioned during the office visit and treatment patterns. The Pain Panel supplement surveys over 115 pain specialist physicians each month. With the inclusion of visits to pain specialists, this will allow additional insight into the pain market. The data are then projected nationally by physician specialty and region to reflect national prescribing patterns.

4.2 DRUG UTILIZATION DATA TABLES

Table 60. National estimates of prescriptions dispensed for IR and ER CII stimulants from U.S. outpatient retail pharmacies from the second quarter of 2014 through the fourth quarter of 2019

	Q2 2014	Q3 2014	Q4 2014	Q1 2015	Q2 2015	Q3 2015	Q4 2015	Q1 2016	Q2 2016	Q3 2016	Q4 2016	
Grand Total	11,659,628	11,608,205	12,469,883	12,534,914	12,443,563	12,397,053	13,248,151	13,487,420	13,204,066	13,082,371	13,828,729	
Extended-release CII stimulants	6,448,323	6,303,338	6,908,123	6,932,134	6,743,774	6,614,590	7,197,693	7,329,120	7,023,981	6,862,422	7,400,334	
Immediate-release CII stimulants	5,211,305	5,304,867	5,561,760	5,602,780	5,699,789	5,782,463	6,050,458	6,158,300	6,180,085	6,219,949	6,428,395	
	Q1 2017	Q2 2017	Q3 2017	Q4 2017	Q1 2018	Q2 2018	Q3 2018	Q4 2018	Q1 2019	Q2 2019	Q3 2019	Q4 2019
Grand Total	13,545,833	13,219,569	12,936,529	13,808,315	13,623,481	13,499,576	13,142,677	13,915,607	13,831,698	13,684,532	13,588,358	14,281,858
Extended-release CII stimulants	7,170,480	6,866,534	6,654,895	7,289,451	7,123,205	6,931,382	6,637,317	7,189,643	7,138,320	6,909,122	6,755,333	7,280,343
Immediate-release CII stimulants	6,375,353	6,353,035	6,281,634	6,518,864	6,500,276	6,568,194	6,505,360	6,725,964	6,693,378	6,775,410	6,833,025	7,001,515

IR, immediate-release; ER, extended-release; CII, Schedule II; U.S., United States.

Source: FDA analysis of IQVIA, National Prescription Audit™. 2014–2019. Extracted March 2020. File: 2020-95 NPA stimulants TRx IR vs ER NPA Mar-11-2020.xlsx.

Table 61. National estimates of prescriptions dispensed for CII stimulants, stratified by drug, from U.S. outpatient retail pharmacies from the second quarter of 2014 through the fourth quarter of 2019

	Q2 2014	Q3 2014	Q4 2014	Q1 2015	Q2 2015	Q3 2015	Q4 2015	Q1 2016	Q2 2016	Q3 2016	Q4 2016	
Grand Total	13,677,230	13,599,998	14,571,319	14,660,601	14,559,553	14,510,175	15,501,758	15,792,349	15,486,649	15,320,122	16,183,981	
Mixed Amphetamine Salts	6,318,239	6,415,055	6,756,147	6,835,797	6,971,395	7,062,798	7,409,316	7,546,829	7,596,265	7,629,297	7,897,665	
Methylphenidate	3,796,535	3,689,447	4,003,894	3,981,442	3,819,114	3,689,426	4,004,032	4,064,724	3,861,990	3,704,771	3,987,609	
Lisdexamfetamine	2,432,004	2,410,205	2,613,798	2,641,487	2,626,426	2,640,340	2,842,771	2,902,587	2,824,758	2,804,315	2,991,711	
Dexmethylphenidate	930,909	886,984	993,569	1,003,353	936,805	906,508	1,023,258	1,055,381	979,285	947,328	1,050,592	
Dextroamphetamine	196,495	195,331	200,925	194,664	195,779	195,153	200,070	199,018	199,047	204,085	218,692	
Amphetamine	—	—	—	1,089	7,128	13,176	19,673	21,301	22,757	27,879	35,197	
Methamphetamine	3,048	2,976	2,986	2,769	2,906	2,774	2,638	2,509	2,547	2,447	2,515	
	Q1 2017	Q2 2017	Q3 2017	Q4 2017	Q1 2018	Q2 2018	Q3 2018	Q4 2018	Q1 2019	Q2 2019	Q3 2019	Q4 2019
Grand Total	15,954,294	15,598,575	15,191,341	16,174,164	16,062,339	15,995,258	15,620,809	16,521,933	16,453,637	16,376,169	16,359,950	17,191,478
Mixed Amphetamine Salts	7,841,964	7,863,439	7,780,601	8,113,348	8,133,107	8,294,121	8,229,153	8,526,672	8,533,852	8,661,246	8,754,129	9,008,477
Methylphenidate	3,923,528	3,699,129	3,499,131	3,811,628	3,735,106	3,592,488	3,407,561	3,690,970	3,671,265	3,564,097	3,492,519	3,790,853
Lisdexamfetamine	2,890,745	2,807,720	2,722,606	2,911,436	2,828,463	2,802,421	2,728,856	2,910,264	2,840,755	2,814,878	2,804,976	2,956,084
Dexmethylphenidate	1,041,929	960,439	916,397	1,039,453	1,066,301	1,004,130	960,446	1,082,175	1,107,907	1,045,839	1,023,719	1,142,796
Dextroamphetamine	216,526	223,996	227,638	242,457	236,478	239,160	236,634	247,929	237,244	232,815	232,461	238,291
Amphetamine	37,450	41,534	42,684	53,464	60,724	60,748	56,059	61,801	60,634	55,343	50,105	52,934
Methamphetamine	2,152	2,318	2,284	2,378	2,160	2,190	2,100	2,122	1,980	1,951	2,041	2,043

CII, Schedule II; U.S., United States.

Source: FDA analysis of IQVIA, National Prescription Audit™. 2014–2019. Extracted March 2020. File: 2020-95 NPA stimulants by molecule_1_Mar-24-2020.xlsx.

Table 62. National estimates of prescriptions dispensed for IR racemic amphetamine sulfate, stratified by drug strength, from U.S. outpatient retail pharmacies, in 2019

Molecule	Strength	2019	
		TRx (N)	Share (%)
Amphetamine sulfate	Total	88,698	100.0%
	10mg	71,390	80.5%
	5mg	15,986	18.0%
	20mg	827	0.9%
	15mg	495	0.6%

IR, immediate-release; U.S., United States.

Source: FDA analysis of IQVIA, National Prescription Audit™. 2019. Extracted July 2020. File: 2020-95 NPA racemic amphetamine strength 2019.xlsx.

Table 63. National estimates of prescriptions dispensed for IR amphetamines or ER amphetamines, stratified by patient age, from U.S. outpatient retail pharmacies, January 2018 through December 2019

	IR amphetamines	ER amphetamines
Total	42,059,090	29,652,907
<3 years	478	383
3 to 9 years	1,434,619	2,206,497
10 to 19 years	3,914,281	7,710,950
20 to 39 years	21,412,938	12,048,691
40 to 59 years	12,390,213	6,299,975
60 to 64 years	1,491,954	728,488
65 to 74 years	1,196,128	541,589
75 to 84 years	154,778	65,010
85+ years	18,590	8,975
Unspecified	45,589	42,732

IR, immediate-release; ER, extended-release; U.S., United States.

Source: FDA analysis of IQVIA, National Prescription Audit™. 2018-2019. Extracted July 2020. File: 2020-95 NPA amphetamine ir vs er by age Jul-09.xlsx.

Table 64. National estimates of prescriptions dispensed for CII stimulants, stratified by patient age (<20 years, 20-64 years, and 65+ years), from U.S. outpatient retail pharmacies, January 2008 through December 2019

	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019
Grand Total	31,238,203	32,992,801	36,061,179	38,770,820	40,124,778	42,822,663	45,336,497	48,599,626	51,383,665	51,575,411	52,963,814	55,005,075
<20 Years	18,995,774	18,821,733	19,484,975	20,135,109	19,843,565	20,494,010	20,811,938	21,287,039	21,665,207	20,966,844	20,653,999	20,736,194
20-64 Years	11,770,905	13,649,043	15,985,801	17,969,289	19,535,656	21,498,084	23,571,820	26,246,016	28,493,291	29,300,572	30,857,816	32,661,437
65+ Years	471,524	522,025	590,403	666,422	745,558	830,569	952,738	1,066,571	1,225,168	1,307,995	1,451,999	1,607,445

CII, Schedule II; U.S., United States.

Source: FDA analysis of IQVIA, National Prescription Audit Patient Insights™. 2008-2019. Extracted April 2020. File: 2020-95 NPA stimulants by age Apr-2020.xlsx.

Table 65. National estimates of patients who received dispensed prescriptions for CII stimulants, stratified by patient age (<6 years, 6-12 years, 13-19 years, 20-39 years, 40-59 years, 60+ years), from U.S. outpatient retail pharmacies, January 2008 to December 2019

	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019
Grand total	6,324,871	6,537,523	7,102,287	8,248,603	8,071,604	8,178,142	8,480,775	8,677,665	9,152,922	9,160,843	8,954,481	9,177,551
<6 years	97,072	93,219	96,626	101,591	91,816	87,225	103,969	95,375	87,826	77,567	71,817	67,518
6 - 12 years	2,022,584	1,985,033	2,073,498	2,257,831	2,141,433	2,127,670	2,168,843	2,178,479	2,162,278	2,056,290	1,939,894	1,915,948
13 - 19 years	1,675,310	1,675,368	1,744,604	1,929,653	1,861,410	1,855,225	1,877,500	1,913,269	1,906,038	1,846,768	1,787,018	1,810,485
20 - 39 years	1,424,293	1,606,072	1,868,998	2,369,853	2,431,364	2,519,150	2,762,341	2,959,222	3,152,138	3,180,394	3,134,724	3,220,227
40 - 59 years	839,796	912,893	1,038,960	1,248,824	1,251,002	1,282,899	1,422,345	1,551,524	1,641,726	1,699,490	1,677,400	1,784,603
60+ years	187,492	204,004	232,847	276,190	287,133	322,789	407,832	442,731	442,767	453,664	453,136	485,909
Unknown age	300,842	281,337	207,129	256,996	109,896	491,648	314,305	77,427	14,891	77,625	27,869	14,080

CII, Schedule II; U.S., United States.

Note: Patient age subtotals may not sum exactly due to patients aging during the study period and may be counted more than once in the individual age categories. For this reason, summing across time periods or patient age bands is not advisable and will result in overestimates of patient counts.

Source: FDA analysis of IQVIA, Total Patient Tracker™. 2008-2019. Extracted March 2020. File: 2020-95 TPT Stimulant group 2008-2019 report.xlsx.

Table 66. National estimates of prescriptions dispensed for CII opioid analgesics or CII stimulant products, from U.S. outpatient retail pharmacies, January 2015 through December 2019

	2015	2016	2017	2018	2019	
Total	229,945,245	100%	223,241,927	100%	205,596,917	100%
CII stimulants	59,584,420	26%	62,966,572	28%	63,034,818	31%
CII opioid analgesics	170,360,825	74%	160,275,355	72%	142,562,099	69%

CII, Schedule II; U.S., United States.

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

Source: FDA analysis of IQVIA, National Prescription Audit™. 2019. Extracted July 2020. File: 2020-95 NPA stimulants vs opioids.xlsx.

Table 67. Nationally estimated number of prescriptions dispensed for opioid analgesic products from U.S. outpatient retail pharmacies, January 2006 through December 2019

	2006	2007	2008	2009	2010	2011	2012	
Grand Total of Opioid Analgesics	224,002,463	100%	235,752,402	100%	244,540,733	100%	249,938,575	100%
Immediate -Release Market*	204,982,001	92%	214,741,765	91%	222,234,178	91%	227,210,783	91%
Extended-Release/Long-Acting Market**	19,020,462	8%	21,010,637	9%	22,306,555	9%	22,727,792	9%
Abuse-Deterrent Formulations***	0	0%	0	0%	0	0%	14,106	1%
	2013	2014	2015	2016	2017	2018	2019	
Grand Total of Opioid Analgesics	251,753,771	100%	244,463,305	100%	227,785,440	100%	215,970,206	100%
Immediate -Release Market*	229,574,767	91%	222,448,389	91%	206,318,188	91%	195,536,437	91%
Extended-Release/Long-Acting Market**	22,179,004	9%	22,014,916	9%	21,467,252	9%	20,433,769	9%
Abuse-Deterrent Formulations***	4,850,154	2%	4,686,484	2%	4,519,991	2%	4,264,525	2%

ER, extended-release; IR, immediate-release; U.S., United States.

Note: ** Immediate-Release formulations include oral solids, oral liquids, rectal, nasal, and transmucosal formulations

Note: *** Extended-Release/Long-Acting formulations include oral solids and transdermal patches

Note: **** Abuse-deterrent formulation opioid products include Arymo ER, Embeda ER, Hysingla ER, Morphabond ER, Xtampza ER, OxyContin ER Reformulated (Approval in April 2010), RoxyBond IR.

Note: These data include non-injectable opioid analgesics only. Opioid-containing cough-cold products and opioid-containing medication-assisted treatment (MAT) products are not included.

Source: FDA analysis of IQVIA, National Prescription Audit (NPA) and static data 2006-2011. January 2006-December 2019. Static data extracted March 2017, 2012-2017 data extracted February 2018, 2018 data extracted March 2019, 2019 data extracted Jan 24, 2020.

4.3 FDA ADVERSE EVENT REPORTING SYSTEM DESCRIPTION

FAERS is a database that contains information on AE and medication error reports submitted to FDA. The database is designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. AEs and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary.

FAERS data have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every AE or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an AE or medication error in the U.S. population.

4.4 PREFERRED TERMS IN *DRUG ABUSE AND DEPENDENCE (SMQ) BROAD SEARCH (MEDDRA VERSIONS 19.1, 23.0)*

Accidental overdose
Cannabinoid hyperemesis syndrome*
Delusion of parasitosis*
Dependence
Disturbance in social behaviour
Dopamine dysregulation syndrome
Drug abuse
Drug abuser
Drug dependence
Drug dependence, antepartum
Drug dependence, postpartum
Drug detoxification
Drug diversion
Drug level above therapeutic
Drug level increased
Drug screen
Drug screen positive
Drug tolerance
Drug tolerance decreased
Drug tolerance increased
Drug use disorder*
Drug use disorder, antepartum*
Drug use disorder, postpartum*
Intentional overdose
Intentional product misuse
Intentional product use issue
Maternal use of illicit drugs
Medication overuse headache
Narcotic bowel syndrome
Needle track marks
Neonatal complications of substance abuse
Overdose

Performance enhancing product use*
 Prescription drug used without a prescription
 Prescription form tampering
 Reversal of opiate activity
 Substance abuse
 Substance abuser
 Substance dependence
 Substance use
 Substance use disorder*
 Substance-induced mood disorder
 Substance-induced psychotic disorder
 Toxicity to various agents

Note: '*' Preferred Terms in MedDRA version 23.0 not in MedDRA version 19.1

4.5 FAERS CASE NUMBERS, FAERS VERSION NUMBERS, AND MANUFACTURER CONTROL NUMBERS OF NONMEDICAL CII PRESCRIPTION STIMULANT USE VIA NON-ORAL ROUTE (N=188)

CII Prescription Stimulant	FAERS Case #	Version Number	Manufacturer Control #
Methylphenidate	6246076	1	PHBS2007DK03172
	6299688	1	PHEH2007US06105
	6409392	2	PHNU2007DE03031
	6556818	1	PHBS2008CH02117
	6575005	2	PHHY2008JP02322
	6587171	1	PHHY2008JP02329
	6723904	1	PHHY2008DK16538
	6742027	1	PHBS2008IL05488
	6749404	1	PHHY2008FR19844
	6770955	1	US-JNJFOC-20080905034
	6932200	2	PHHY2009NO08127
	6943570	1	PHHY2009DK08720
	6958196	1	PHHY2009AU11479
	7080299	1	FI-JNJFOC-20090801069
	7147787	1	PHHY2009DK42360
	7148823	1	FI-JNJFOC-20091003603
	7177137	1	PHHY2009FR48736
	7351602	1	PHHY2010US20998
	7392897	3	PHHY2010DE27963
	7406257	1	US-TYCO HEALTHCARE/MALLINCKRODT-T201001323
	7406268	1	US-TYCO HEALTHCARE/MALLINCKRODT-T201001317
	7406269	1	US-TYCO HEALTHCARE/MALLINCKRODT-T201001324
	7406270	1	US-TYCO HEALTHCARE/MALLINCKRODT-T201001322
	7487040	1	PHHY2010FR45218
	7630481	1	ZA-JNJFOC-20101002828

CII Prescription Stimulant	FAERS Case #	Version Number	Manufacturer Control #
	7874252	1	US-TYCO HEALTHCARE/MALLINCKRODT-T201100609
	7940433	2	FI-JNJFOC-20110411818
	7973871	1	PHHY2011IS46015
	8011433	1	CA-PURDUE-CAN-2011-0002058
	8167675	2	PHHY2011DE86650
	8182726	1	GB-JNJFOC-20111002816
	8271449	1	CH-COVIDIEN/TYCO HEALTHCARE/MALLINCKRODT-T201102771
	8275660	1	CH-COVIDIEN/TYCO HEALTHCARE/MALLINCKRODT-T201102786
	8284440	1	2011MA016798
	8284462	1	2011MA016797
	8284651	1	2011MA016792
	8437283	1	FI-JNJFOC-20120211510
	8450864	2	NZ-JNJFOC-20120214056
	8525609	1	US-COVIDIEN/TYCO HEALTHCARE/MALLINCKRODT-T201200796
	8533253	1	PHHY2012FR033461
	8637624	3	PHHY2012FR053966
	8767520	1	PHHY2012US076205
	8909049	2	PHHY2012CH104705
	9099663	1	CA-JNJFOC-20130116689
	9250866	1	PHHY2013CH036239
	9278220	1	PHHY2013FR044716
	9352039	1	PHHY2012NL112469
	9364574	2	PHHY2013FR064274
	9377076	1	SE-JNJFOC-20130611329
	9475670	1	PHHY2013FR091266
	9476354	1	FI-JNJFOC-20130810154
	9493354	1	PHHY2013FR094870
	9493356	1	PHHY2013FR094842
	9494661	1	MX-JNJFOC-20130816797
	9788796	2	PHHY2013SE143121
	9832133	1	SE-JNJFOC-20140106195
	9993137	2	PHHY2014SE028117
	10057280	1	PHHY2014ES040082
	10070341	1	PHHY2014AU040966
	10098579	1	US-MALLINCKRODT-T201401876
	10163445	3	PHHY2014FR050197
	10223832	3	SE-JNJFOC-20140518480
	10260872	1	PHHY2014ZA078276
	10362536	2	PHHY2014SE095508
	10364626	1	PHHY2014FR094171
	10366333	2	PHHY2014DE094318

CII Prescription Stimulant	FAERS Case #	Version Number	Manufacturer Control #
	10447735	1	PHHY2014IS112761
	10460997	1	PHHY2014US119782
	10514971	1	PHEH2014US020040
	10601740	2	PHHY2014FR149135
	10601742	1	PHHY2014FR148976
	10601746	1	PHHY2014FR149020
	10603102	2	PHHY2014FR149087
	10606352	1	PHHY2014FR149085
	10644146	1	SE-JNJFOC-20141204833
	10646806	1	SE-JNJFOC-20141204841
	10660513	1	US-NAPPmundi-USA-2014-0116001
	10674033	1	PHHY2014IL166163
	10803943	1	PHHY2015SE018210
	10929223	2	US-JNJFOC-20131016944
	10992329	1	PHHY2015IL037215
	11153785	1	US-NOVEN PHARMACEUTICALS, INC.-14US009739
	11216906	1	Direct Report
	11226423	1	PHHY2015FR077562
	11675111	1	ZA-JNJFOC-20151018568
	11722775	4	PHHY2015US143255
	11864559	1	PHHY2015FR167442
	11940855	1	PHHY2016IS007347
	12074289	1	PHHY2016CH018687
	12127055	1	ZA-JNJFOC-20160224630
	12282253	3	CA-JNJFOC-20160413846
	12378782	2	SE-JNJFOC-20160513035
	12495147	1	PHHY2016FR084081
	12504805	1	PHHY2016CH071926
	12546430	2	US-PFIZER INC-2016334276
	12582571	1	PHHY2016FR100368
	12583341	1	PHHY2016FR100212
	12600067	1	PHHY2016FR103079
	12601590	1	PHHY2016FR103199
	12601591	1	PHHY2016FR103188
	12601599	1	PHHY2016FR103189
	12642496	2	US-JAZZ-2016-US-014681
	12732367	1	PHHY2016FR124637
	12773821	1	FR-ROCHE-1833040
	12859799	1	PHHY2016FR142062
	12859808	1	PHHY2016FR141971
	12859815	1	PHHY2016FR141876
	12877332	1	PHHY2016FR144050
	12979844	1	PHHY2016FR162672
	13045560	1	PHHY2016FR173001
	13053934	1	PHHY2016FR173814

CII Prescription Stimulant	FAERS Case #	Version Number	Manufacturer Control #
	13057675	3	ES-SUN PHARMACEUTICAL INDUSTRIES LTD-2016R1-129841
	13070953	1	PHHY2016FR179456
	13117937	1	US-JNJFOC-20161214428
	14271470	1	US-JNJFOC-20171212565
	15451692	1	US-MYLANLABS-2018M1069948
	17619057	1	US-UCBSA-2017031635
Methamphetamine	6446005	1	070928-0000962
	8186440	1	DKLU1073241
	8384009	1	AUR-APL-2012-00361
	8460169	1	DKLU1067864
	13468425	1	US-MUNDIPHARMA DS AND PHARMACOVIGILANCE-USA-2017-0137603
	13989619	1	US-WEST-WARD PHARMACEUTICALS CORP.-US-H14001-17-03490
	14116357	1	US-NAPPmundi-USA-2017-0139040
	14344518	1	US-NAPPmundi-USA-2017-0140813
	14801933	1	US-NAPPmundi-USA-2017-0141566
	14999928	1	US-RECORDATI RARE DISEASES INC.-US-R13005-18-00150
	15179809	1	US-RECORDATI RARE DISEASES INC.-US-R13005-18-00198
	15244974	1	US-NAPPmundi-USA-2018-0144365
	15431214	1	US-INDIVIOR LIMITED-INDV-108176-2018
	15613002	1	US-PFIZER INC-2018464099
	15797255	1	US-JNJFOC-20190101245
	15804376	1	US-PFIZER INC-2019007883
	15824257	1	US-MALLINCKRODT-T201900920
	16102455	1	US-LANNETT COMPANY, INC.-US-2019LAN000866
	16102457	1	US-LANNETT COMPANY, INC.-US-2019LAN000867
	16102458	1	US-LANNETT COMPANY, INC.-US-2019LAN000865
	16819071	2	US-INDIVIOR EUROPE LIMITED-INDV-121522-2019
	16821030	1	US-HIKMA PHARMACEUTICALS USA INC.-US-H14001-19-04935
	16895128	1	US-INDIVIOR LIMITED-INDV-116077-2018
	16980422	1	US-INDIVIOR EUROPE LIMITED-INDV-122149-2019
	17170756	1	US-MALLINCKRODT-T201908066
	17208859	3	US-INDIVIOR US-INDV-121724-2019
	17208954	1	US-INDIVIOR EUROPE LIMITED-INDV-121851-2019
Mixed amphetamine salts	6253324	1	SPV1-2007-00604
	6451967	1	SPV1-2007-04402
	6643929	1	026730
	7437345	2	1-22572182
	8133040	1	US-SHIRE-ALL1-2011-02341

CII Prescription Stimulant	FAERS Case #	Version Number	Manufacturer Control #
	9447696	1	US-SHIRE-ALL1-2013-05327
	10447287	1	US-SHIRE-US201405721
	12295781	1	US-PURDUE PHARMA-USA-2016-0128916
	13544026	1	US-SHIRE-US201710184
	13645358	1	US-IMPAKX LABORATORIES, INC-2017-IPXL-01774
	15465434	2	US-ALLERGAN-1847387US
	15768638	1	US-AUROBINDO-AUR-APL-2018-061823
	17250483	1	US-MALLINCKRODT-T201908667
	17250493	1	US-MALLINCKRODT-T201908652
Amphetamine	9014432	1	US-JNJFOC-20130105003
	9018994	1	US-ABBOTT-13P-163-1036997-00
	13123064	1	US-MALLINCKRODT-T201606950
	13347709	2	US-JAZZ-2017-US-003413
	13657980	1	US-TORRENT-00002959
	14274414	1	US-JNJFOC-20171208884
	14448187	1	US-NAPPUNDI-USA-2018-0142510
	14521668	1	US-ARBOR PHARMACEUTICALS, LLC-US-2018ARB000128
	16470858	1	US-ARBOR PHARMACEUTICALS, LLC-US-2019ARB000992
	16805793	2	US-DRREDDYS-USA/USA/19/0114231
Lisdexamfetamine	7367022	2	SPV1-2010-00626
	9700824	1	US-SHIRE-ALL1-2013-07956
	10785488	1	US-SHIRE-US201501070
	11087473	1	US-SHIRE-US201503823
	12692368	1	US-SHIRE-US201610657
	12695400	1	US-SHIRE-US201610643
	16375159	1	US-SHIRE-US201917503
Dexmethylphenidate	6832407	1	PHEH2008US02111
	6985123	1	PHEH2009US04185
Multiple Prescription Stimulants	7126972	1	2009AP003527
	8054406	2	PHHY2011FR65680
	8301397	1	US-RB-035140-11
	13106600	2	US-TEVA-728481USA
	13721384	1	US-NAPPUNDI-USA-2017-0139680
	13968016	1	US-MYLANLABS-2017M1056467
	14195138	1	US-NAPPUNDI-USA-2017-0141587
	15836164	1	US-INSYS THERAPEUTICS, INC-INS201901-000282
	16004366	1	US-MALLINCKRODT-T201900845
	16805993	1	US-HIKMA PHARMACEUTICALS USA INC.-US-H14001-19-04888
	17188394	1	US-MALLINCKRODT-T201908193

CII, Schedule II; FAERS, FDA Adverse Event Reporting System; FDA, Food and Drug Administration.

Source: FDA Adverse Event Reporting System. Time period from January 1, 2007 to December 31, 2016 searched on March 15, 2017, and time period from January 1, 2017 to April 24, 2020 searched on April 24, 2020.

4.6 AAPCC NPDS: GENERIC CODES, PRODUCT CODES, VARIABLE DEFINITIONS, AND METHODOLOGY FOR ANALYSES

Table 68. AAPCC NPDS methodology for prescription and illicit stimulant categorization

Stimulant Category	Classification Criteria
Prescription Stimulants	
Amphetamine	<ul style="list-style-type: none">• Brand name and/or manufacturer name, strength, etc.
Dextroamphetamine	
Mixed Amphetamine Salts	<ul style="list-style-type: none">• Brand name and/or manufacturer name, strength, etc.
Lisdexamfetamine	<ul style="list-style-type: none">• All associated slang terms*• All associated chemical names without additional manufacturer details*
Methylphenidate	
Dexmethylphenidate	
Methamphetamine	<ul style="list-style-type: none">• Brand name and/or manufacturer name, strength, etc.
Illicit Stimulants	
All Cocaine	<ul style="list-style-type: none">• Brand name and/or manufacturer name, strength, etc.[§]• All associated slang terms• All associated chemical names without additional manufacturer details
Methamphetamine (Illicit)	<ul style="list-style-type: none">• All associated slang terms• All associated chemical names without additional manufacturer details
Other	
Amphetamine (NOS) [‡]	<ul style="list-style-type: none">• All associated slang terms• All associated chemical names without additional manufacturer details
Additional Inclusion and Exclusion Criteria	
Retained Codes	<ul style="list-style-type: none">• Codes describing people (e.g., Raver, Body-packer, First basemen)• Codes describing places where drugs are made• Codes describing residues• Codes describing very rare products that are not currently marketed in the US, but are marketed elsewhere (e.g., alpha-Prodine): Categorized as “prescription”• Codes describing drug withdrawal
Dropped Codes	<ul style="list-style-type: none">• Codes containing references to paraphernalia (e.g., outfits, pipes, etc)• Codes describing places where drugs are consumed (if not other detail captured in the code)• Codes describing the sale of drugs• Codes describing unknown euphoria• Codes describing habitual use (of a specific API) not related to withdrawal• Codes describing non-specific withdrawal (e.g., “Opioid Withdrawal”)

AAPCC, American Association of Poison Control Centers; NPDS, National Poison Data System NOS, Not otherwise specified; FDA, Food and Drug Administration.

Note: '*' indicates slang terms and chemical names tied to prescription stimulant active pharmaceutical ingredient (API) are more likely to be diverted than illicitly manufactured.

Note: '§' indicates prescription cocaine is unlikely to be found outside of the hospital setting, since it is primarily used in the surgical setting. Therefore, all prescription cocaine exposures were treated as illicit cocaine.

Note: '‡' indicates all amphetamine products where it is unclear if the product is a prescription product or illicitly/clandestinely manufactured. Source: FDA.

Table 69. AAPCC NPDS list of stimulant product codes*

Stimulant API	Stimulant Product Codes
Amphetamine	
Dextroamphetamine	
Mixed Amphetamine Salts	

Stimulant API	Stimulant Product Codes
Lisdexamfetamine	
Methylphenidate	

Stimulant API	Stimulant Product Codes
Dexmethylphenidate	
Methamphetamine	
Cocaine	

Stimulant API	Stimulant Product Codes

AAPCC, American Association of Poison Control Centers; NPDS, National Poison Data System; API, active pharmaceutical ingredient.

Note: ** Generic and product codes were redacted for public release.

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

Table 70. AAPCC NPDS list of prescription and illicit opioid, benzodiazepine, muscle relaxant, alcohol, and cannabis generic and product codes*

Substance	Codes
Opioid Product Codes	
Opioid Generic Codes	
Benzodiazepine Generic Codes	
Muscle Relaxant Generic Codes	

Substance	Codes
Alcohol Generic Codes	
Cannabis Generic Codes	

AAPCC, American Association of Poison Control Centers; NPDS, National Poison Data System.

Note: ** Generic and product codes were redacted for public release.

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

Table 71. Expanded AAPCC NPDS variable definitions

Variable	Definition
Exposure Reason	
Unintentional	An unintentional exposure results from an unforeseen or unplanned event. For example, a child gaining access to a toxic substance, when it is obvious the child did not realize the danger of the action, is an unintentional exposure. The following eight categories are available for unintentional exposures: <i>General; Environmental; Occupational; Therapeutic Error; Misuse; Bite/Sting; Food Poisoning; Unknown.</i>
Intentional	
Suspected Suicide	An exposure resulting in the inappropriate use of a substance for self-harm or self-destruction or manipulative reasons.
Abuse	An exposure resulting from the intentional improper or incorrect use of a substance where the victim was likely attempting to gain a high, euphoric effect or some other psychotropic effect, including recreational use of a substance for any effect.
Misuse	An exposure resulting from the intentional improper or incorrect use of a substance for reasons other than the pursuit of a psychotropic effect.
Unknown	Exposures that are deemed to be intentional although the specific motive is undetermined.
Adverse Reaction	
Other/Unknown	This category is used to monitor adverse reactions (experiences) to a variety of products, including drugs, foods, cosmetics and industrial or household chemicals. The following three categories are available for adverse reactions: <i>Drug; Food; Other.</i>
Exposure Route	
Ingestion	An exposure by the oral route. Exposures in which the material was put in the mouth but unlikely to have reached the stomach are also classified as ingestions.
Inhalation/Nasal	An exposure by the pulmonary route (tracheal or nasal). This route usually pertains to gaseous or vaporized agents. This includes nasal insufflation of substances.
Aspiration (with Ingestion)	An exposure by the pulmonary route (tracheal). This route usually pertains to liquid or solid agents and occurs during or following an INGESTION.
Ocular	An exposure involving the eyeball.
Dermal	An exposure involving the skin, hair, or fingernails.

Variable	Definition
Bite/Sting	An exposure resulting from an animal/insect bite or sting with or without envenomation.
Parenteral	An exposure resulting from the injection of a substance into the body.
Other	Any other route of exposure not listed above.
Otic	An exposure to the ear or ear canal with or without perforation of the tympanic membrane.
Rectal	An exposure involving the rectum where the implicated substance was physically placed in, applied to or instilled in the rectum.
Unknown	The route of exposure is unknown.
Vaginal	An exposure involving the vagina where the implicated substance was physically placed in, applied to or instilled in the vagina.
Medical Outcome (known)*	
No Effect	The patient developed no symptoms (clinical effects) as a result of the exposure. Follow-up is required to make this determination unless the initial poison center call occurs sufficiently long enough after the exposure that the poison center is reasonably certain no effects will occur.
Minor Effect	The patient exhibited some symptoms as a result of the exposure, but they were minimally bothersome to the patient. The symptoms usually resolve rapidly and often involve skin or mucous membrane manifestations. The patient has returned to a pre-exposure state of well-being and has no residual disability or disfigurement. Follow-up is required to make this determination unless the initial poison center call occurs sufficiently long enough after the exposure that there is reasonable certainty that the clinical effect(s) will not worsen. Symptomatic patients must be followed until symptoms have resolved or nearly resolved, unless the residual symptoms are anticipated to be long-term and of minimal clinical significance.
Moderate Effect	The patient exhibited symptoms as a result of the exposure which are more pronounced, more prolonged or more of a systemic nature than minor symptoms. Usually some form of treatment is or would have been indicated. Symptoms were not life-threatening and the patient has returned to a pre-exposure state of well-being with no residual disability or disfigurement. Follow-up is required to make this determination unless the initial regional poison center call occurs sufficiently long enough after the exposure that there is reasonable certainty that the clinical effect(s) will not get worse. Symptomatic patients must be followed until symptoms have resolved or nearly resolved, unless the residual symptoms are anticipated to be long-term and of minimal clinical significance.
Major Effect	The patient has exhibited symptoms as a result of the exposure which were life-threatening or resulted in significant residual disability or disfigurement. Follow-up is required to make this determination unless the initial poison center call occurs sufficiently long enough after the exposure that there is reasonable certainty the clinical effect(s) will not get worse. Symptomatic patients must be followed until symptoms have resolved or nearly resolved, unless the symptoms are anticipated to be long-term or permanent.

Variable	Definition
Death	The patient died as a result of the exposure or as a direct complication of the exposure where the complication was unlikely to have occurred had the toxic exposure not preceded the complication. Only include those deaths which are probably or undoubtedly related to the exposure. A fatality verification is required. Also include deaths in which the exposure was a contributing factor in the death. For deaths determined to be unrelated to the exposure (those in which the most clinically significant clinical effects are coded as unrelated) the outcome is coded as “Unrelated effect” (the exposure was probably not responsible for the effect[s]).

AAPCC, American Association of Poison Control Centers; NPDS, National Poison Data System.

Note: '*' Case Followed to Known Outcome: A response is appropriate in this area only if follow-up continues until medical outcome can be documented with reasonable certainty (known outcome). When it is not appropriate or possible to follow a patient to a known or certain outcome, an outcome in the section labeled, “CASE NOT FOLLOWED TO KNOWN OUTCOME” Is used. There is also an option provided for those cases in which the exposure was probably not responsible for the effect(s).

Source: American Association of Poison Control Centers. National Poison Data System (NPDS) Data Dictionary. Version 2016.07.11. July 11, 2016.

Table 72. AAPCC NPDS United States region categorization

Region	U.S. States, District of Columbia, and Other Locations
Northeast	Connecticut, Maine, Massachusetts, New Hampshire, New Jersey, New York, Pennsylvania, Rhode Island, Vermont
South	Alabama, Arkansas, Delaware, District of Columbia, Florida, Georgia, Kentucky, Louisiana, Maryland, Mississippi, North Carolina, Oklahoma, South Carolina, Tennessee, Texas, Virginia, West Virginia
Midwest	Illinois, Indiana, Iowa, Kansas, Michigan, Minnesota, Missouri, Nebraska, North Dakota, Ohio, South Dakota, Wisconsin
West	Alaska, Arizona, California, Colorado, Hawaii, Idaho, Montana, Nevada, New Mexico, Oregon, Utah, Washington, Wyoming
Other Locations	American Samoa, Guam, Northern Marianas, Other U.S. Territory, Overseas U.S. military/diplomatic, Puerto Rico, Refused to Give, U.S. Virgin Islands, Unknown

AAPCC, American Association of Poison Control Centers; NPDS, National Poison Data System.

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

4.7 NEISS-CADES: DEFINITIONS

Table 73. Definitions for intent of drug use

Intent of drug use	Definition
Non-medical	Nonmedical use includes pharmaceutical abuse, therapeutic misuse, and overdoses without indication of intent. Abuse cases involve documented clinician diagnosis of abuse or documented recreational use (e.g., “to get high”). Therapeutic misuse cases involved documented therapeutic intent, but use was not as directed (e.g., taking someone else’s prescription medication for pain, intentionally taking larger doses than prescribed). Cases of overdose without indication of intent lack documentation of therapeutic intent, abuse, or self-harm (e.g., patients found unresponsive by paramedics and patients unable or unwilling to provide description of circumstances or intent).
Therapeutic	Therapeutic use includes adverse effects, allergic reactions, supratherapeutic effects, and medication errors.
Self-harm	Self-harm includes administration of pharmaceuticals to injure or kill oneself.

NEISS-CADES, National Electronic Injury Surveillance System – Cooperative Adverse Drug Event Surveillance.

Source: Geller AI, Dowell D, Lovegrove MC, McAninch JK, Goring SK, Rose KO, Weidle NJ, Budnitz DS. U.S. Emergency Department Visits Resulting From Nonmedical Use of Pharmaceuticals, 2016. *Am J Prev Med.* 2019; 56 (5): 639-647. doi: 10.1016/j.amepre.2018.12.009. Epub 2019 Mar 6.

4.8 DRUG-INVOLVED MORTALITY DATA SOURCE AND SEARCH TERMS

4.8.1 Data Source Description

The drug-involved mortality data combine the cause-of-death, demographic, and geographic information from the National Vital Statistics System – Mortality files, with drug-involved mortality information extracted from the death certificate literal text. The analytical dataset was constructed for analysis on October 6, 2016. The method used to extract information on drug-involved mortality has been described previously⁷⁸ and is briefly described here. The information written on the death certificate by the medical certifier on the cause, manner, circumstances, and other factors contributing to the death is referred to as the literal text fields. The literal text information had been processed to allow for the identification of cases of drug-involved mortality, i.e., mortality cases having at least one literal text mention of a drug, drug class, or exposure not otherwise specified, excluding mentions where information in the literal text suggests that the drug was not involved in the death. For example, the drug “METHICILLIN” in the phrase “METHICILLIN RESISTANT STAPHYLOCOCCUS AUREUS INFECTION” does not suggest drug involvement in mortality, but rather a type of bacterial infection. Similarly, the phrase “NOT DRUG RELATED” clearly indicates that a death did not involve drugs.

Although the drug-involved mortality data overcome a major limitation of the current coding system for mortality data by enabling the identification of specific drugs, the drug-involved mortality data have other limitations and considerations. These limitations and considerations are described in more detail elsewhere.⁷⁸ Most importantly, the quality of data extracted from death certificates depends on the amount and level of detail provided by medical certifiers, and such information can vary by certifier, jurisdiction, and over time. For example, the percent of drug overdose deaths with at least one mention of a specific drug has improved from 67% in 2010 to 78% in 2014.⁷⁹ Undercounting of deaths with involvement of specific drugs is likely with the drug-involved mortality data.

4.8.2 Search Terms

Table 74. Search terms used to identify drug mentions in the death certificate literal text

Drug of interest	Search terms used to identify drug of interest
Amphetamine	ADDERALL, AMPHET, AMPHETAMIN, AMPHETAMINE
Dexmethylphenidate	DEXMETHYLPHENIDATE
Dextroamphetamine	ADDERALL, D AMPHETAMINE, DEXTROAMPHETAMINE
Lisdexamfetamine	LISDEXAMFETAMINE
Methamphetamine	MEPHAMPHETAMINE, METAMPHET, METAMPHETAMINE, METH, METHAMPHETAMINE, METHAMPHETAMINESAN, METHAMPHINE, METHAMPLETAMINE, METHAPMHEATMINE, METHYLAMPHETAMINE
Methylphenidate	METHYLOPHENIDATE, METHYLPHENDATE, METHYLPHENIDATE, METTYLPHENIDATE

Source: FDA.

⁷⁸ Trinidad JP, Warner M, Bastian BA, Minino AM, and Hedegaard H. Using literal text from the death certificate to enhance mortality statistics: Characterizing drug involvement in deaths. *Natl Vital Stat Rep.* 2016; 65 (9): 1-15.

⁷⁹ Warner M, Trinidad JP, Bastian BA, Minini AM, and Hedegaard H. Drugs most frequently involved in drug overdose deaths: United States, 2010–2014. *National Vital Statistics Reports.* 2016; 65 (10). Hyattsville, MD: National Center for Health Statistics.