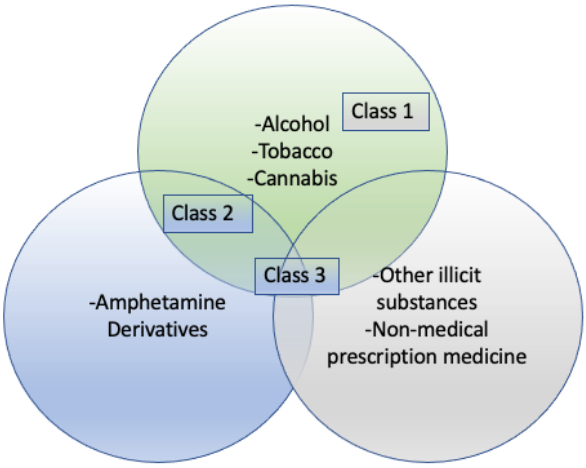
Polysubstance Use



New Mexico Statewide Epidemiological Outcomes Workgroup
White Paper Series

Produced by Coop Consulting, Inc.
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The cover image is a recreation of a visualization of Connor et al.'s Polysubstance Use: Diagnostic Challenges, Patterns of Use, and Health, 2014. This image conceptually depicts classes of substance use patterns from a 2013 large-scale international survey of substance use. The three classes are in order of increasing substance involvement, and the bubbles are not to scale.
Image credit: Coop Consulting, Inc.

Mission New Mexico's Statewide Epidemiological and Outcomes Workgroup (SEOW) reviews and disseminates data about substance abuse and misuse and their consequences. It also identifies best practice information about evidence-based prevention strategies, policies and practices that can lead to successful outcomes for New Mexicans. The purpose of this two-fold work is to inform communities so that they can better target behaviors and risk factors that can be positively impacted by the implementation of well-chosen, evidence-based prevention approaches that are appropriate for the population. The important work of the SEOW is directed by the Office of Substance Abuse Prevention (Behavioral Health Services Division, Human Services Department) and supported by federal funding from the Center for Substance Abuse Prevention, Substance Abuse and Mental Health Services Administration.

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Abstract:

This SEOW white paper is intended to contribute to an understanding of polysubstance use and its consequences. While polysubstance use has been practiced for thousands of years, the majority of substance abuse prevention efforts have generally focused on single-substance issues. This white paper discusses how western medicine has approached substance use disorders, motivations for using multiple substances, and research methodologies used to understand polysubstance use. This paper highlights examples of these methodologies and their significance in adult and youth populations. The examples magnify a need to adapt data collection tools to shift away from single-substance issues towards real-world polysubstance use issues.

Introduction

Polysubstance use is the practice of using more than one licit or illicit substances together.[i] Similar to polysubstance, the current definition of polypharmacy is the act of taking multiple prescription medications more often or in larger quantities than prescribed. For the purpose of this paper, the polypharmacy of prescribed benzodiazepines, opioids, and stimulants will be included in the discussion of polysubstance use.[ii] Polysubstance use has been associated with adverse outcomes that include poorer physical and mental health, increased risk of sexually transmitted diseases, poor cognitive function, and overdose.[iii] Polysubstance use is nebulous, but the concepts described in this paper can be used to clarify the subject.

Background

The oldest psychoactive substances recorded in history are opioids, cannabis, alcohol and cocaine. These substances have been used both independently and together for thousands of years.[iv] Their use is influenced by culture, religion, industrialization, and politics. Despite its historical prevalence, polysubstance use is relatively new to modern substance use research. There are comparatively more tools developed to understand single-substance use behaviors than real-world multiple-substance use behaviors by individuals.

The modern history of substance use disorders began in 1952 when it was included in the first Diagnostic and Statistical Manual of Mental Disorders (DSM)[v]. Since its introduction to the DSM, clinical and researcher attitudes towards substance use disorder have rapidly evolved through evidential research in five different editions. Substance use has been historically catalogued and described in the DSM according to singular substance use, such as alcohol use, cannabis use, opioid use, and stimulant use. “Polysubstance use” was first added to the DSM IV, but was removed in DSM V in favor of a “substance use disorder” diagnosis based on a severity scale from 2-11[vi]. As the DSM shifts away from singular substances in DSM I-III towards understanding how and why substances are used together in DSM IV and V[vii], there is a need to evolve instruments to understand real-world use patterns.[viii]

While sequential or simultaneous use of multiple substances is most often observed in the real-world, polysubstance use is most often researched as a concurrent pattern.[ix] While these words have similar meaning, they are different in the context of substance use. Concurrent use implies using substances over a period of time and simultaneous use indicates that substances were used at the same point in time. This has contributed to a gap in development of effective evidence-based strategies to understand and prevent real-world patterns of polysubstance use.[xxi]

A person-centered modern research method called “class analysis” uses statistical modeling from survey data to reveal classes, or patterns of hidden correlates of subgroups.[xiixiii] When applied to substance use, these analyses have led to useful identification of protective and risk factors, insights into motivation to use multiple substances together, and personalization of substance use prevention and harm reduction messages.[xiv]

Motivations for Polysubstance Use

The reasons people choose to use multiple substances together vary from medical, to recreational, to spiritual. Substances can be used to achieve additive or supraadditive effects to enhance the euphoria of other substances, or antagonistically relieve the negative effects of other substances. Understanding motivations for substance use is an important part of changing behaviors.

Sometimes people are motivated to use multiple substances by a drive for new experiences, or to feel rewarded by opportunistic access.[xv]

Victoria Votaw, a University of New Mexico researcher of polysubstance use treatment, stated that three main reasons for polysubstance use are related to unaddressed medical issues of anxiety, pain, and insomnia.[xvi]

A 2018 *Drug and Alcohol Dependence* journal published a paper that explored the motivations to use methamphetamines and opioids concurrently.[xvii] It found that of 145 participants who self-reported this combination, 51% were “high-seeking”, 38.6% were seeking “balance of effect”, 15.2% reported “available as an opioid substitute”, 9.7% reported “escape from life”, 9% attributed “addiction”, and 6.2% reported that their motivation to use was “social”.

Another reason that could contribute to polysubstance use is the drive to feel “normal.” Exposure to chronic stressors such as long-term abuse and trauma have significant potential to condition one’s brain chemistry to function at a level where substances stabilize emotional regulation or give an individual a perception of emotional regulation.[xviii] This change of brain chemistry is created by upregulation of brain receptors to uptake the stress hormone cortisol, resulting in an imbalanced or blunted response to stress. Upregulation refers to the body’s production of more receptors, in this case, cortisol receptors, to meet the hormone’s plentiful presence resulting from chronic stressors. (See Appendix B for medical definitions)

There is also a need to differentiate intentional polysubstance use from unintentional polysubstance use. Many single-substance users have been exposed to multiple unknown substances through adulteration of the individual’s preferred substance. For instance, during the COVID pandemic,

there were anecdotal reports of illicitly manufactured fentanyl (IMF) found in methamphetamine, heroin, and benzodiazepines that are waiting to be confirmed. Furthermore, for some users, unintentional fentanyl use has resulted in a preference shift for fentanyl.

A discussion about motivations of polysubstance use would be remiss without an economic lens addressing availability. Substance users often unwittingly engage in cost/benefit analysis in making decisions about price, value, effort, and cost. For instance, as the illicit market of opioids shrinks under stricter prescribing, many customers are deciding to opt for other risky substances that are more available at a lower cost and are best used in combination with other substances to mitigate undesired effects.[xix] While economic and behavioral theory are beyond the scope of this white paper, their role in substance use decisions is undeniable and plays an important role in prevention and treatment.

Class Analysis

The statistical method that is proving instrumental in understanding patterns of polysubstance use is class analysis. Class analysis has been used to reveal hidden correlates of reported substance combinations along with demographics, behaviors, or other predictors.[xxxxi] The methods of analysis that seem to be the most powerful at revealing unobservable combination patterns are latent class analysis and hierarchical class analysis. Latent class analysis seems to be more appropriate for a larger sample size while hierarchical class analysis is better suited for smaller sample sizes. Further differences between the two types of analyses are beyond the scope of this white paper.

The number of classes observed in polysubstance use analyses vary, often from three to five classes of distinct substances used together, possibly described by frequency or other patterns of use.[xxii] It's likely that the number of classes will vary by geography and sample populations. These classes could be used to hone prevention and harm reduction messaging for people who use specific substance use combinations, as substance use prevention targets interventions for certain populations with specific risk factors or behaviors.[xxiii]

For instance, it is reasonable to assume that substance use analysis results, including protective and risk factors, would be different between one country's weighted national sample population and a sample population of adolescent females in a treatment center located in a United States metropolis.

Applying Class Analysis to Polysubstance Use

The *Drug and Alcohol Dependence* journal published an article in 2018 that investigated polysubstance use among adult heroin users in Cleveland, Ohio, using cluster and latent class analysis and to describe subpopulations with distinct patterns of polysubstance use using demographic and motivational correlates. The study surveyed 200 heroin-using syringe exchange participants in 2016.

The survey collected information about demographics, employment/income, lifetime and past 30-day frequency of drug use, locations of use, treatment history, HIV/HCV risk, and how substances were obtained. The questions addressed heroin, methamphetamine, crack, powder cocaine, prescription opioid pills, marijuana and alcohol use. The survey probed substance combinations, simultaneous, concurrent use, distress of not having access to the substance, and how much they liked the substance.

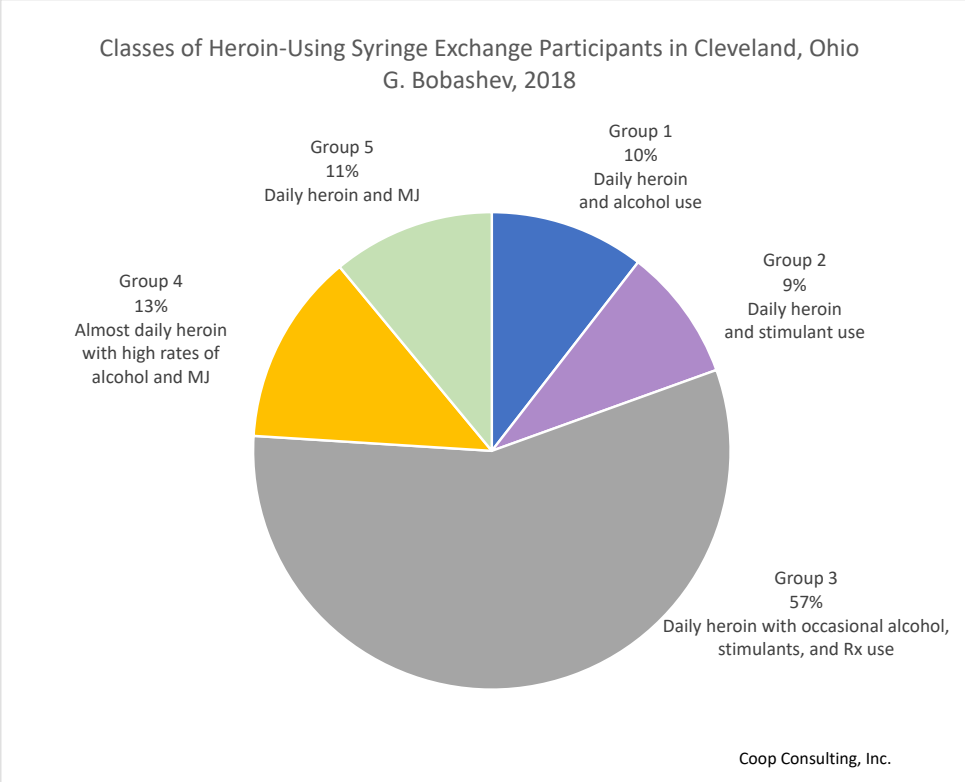
The study identified five distinct clusters to describe Cleveland's heroin users. (Graph 1) This study has limited application to New Mexico's polysubstance users; however, it provides a small example of what latent class analysis can offer should New Mexico pursue surveying polysubstance users. While the full review of what all of the groups or classes of heroin users had in common was not provided, some information about group commonalities and messaging was included in the discussion of the paper.

Group 1 consisted of almost daily alcohol and heroin use, with high rates of stimulants and prescription substance use. (See Graph 1) Group 2 consisted of daily heroin use and almost daily stimulant use. Group 3 consisted of almost daily heroin use, with occasional stimulant, alcohol, or prescription misuse. Group 4 consisted of near daily heroin use with high rates of alcohol and marijuana use. Group 5 consisted of people who daily use heroin and marijuana, with high rates of alcohol use.

Included in the study were the percentages of heroin users reporting frequency of past-month single-substance use, frequency of past-month dual-substance use, and frequency of past month triple-substance use by the five groups. See the three bubble charts of Appendix A Graphs 3, 4 and 5 for past month frequencies of reported use of heroin, methamphetamine, marijuana, alcohol, crack, cocaine, and prescription pills (respondents indicated these included benzodiazepines, however the study clarified this category consisted of prescription opioids) by the five distinct user groups.

One observation suggested that daily substance users with high distress when the substance was unavailable do not change behavior based on perceived risk of cost, health, or arrest. Those with occasional substance use may be more responsive to economics and behavioral theory. Group 1 was older on average than the rest of the groups, averaging 45.8 years, compared to groups 2-5, respectively 33.4, 38.3, 39.05, and 38.0. Group 2 was younger on average than the other groups, more educated, and contained a higher proportion of Latinos.

Graph 1: The five classes or groups of heroin users in Cleveland, OH.



Youth Polysubstance Use

National

One research paper published in 2019 studied youth ages 15-17 in the United States using latent class analysis, finding five different clusters to describe youth substance use in the past 12 months.[xxiv] The first and largest class were the "abstainers" at 67.3%. Class 2, alcohol users at 19.2%. Class 3 was comprised of alcohol, marijuana, and tobacco users, where youth were more likely to use alcohol and marijuana than tobacco products, at 8.2%. Class 4 consisted of alcohol, marijuana, and tobacco users, where youth were more likely to use tobacco than alcohol and marijuana at 3.9%. Class 5 was found to use alcohol, marijuana, tobacco, and other drugs. It was the smallest observed class at 1.4%, but was quite revealing in its analysis. Appendix D contains graphs to depict classes and latent correlates the study produced as the following paragraph discusses.

Class 5 had "higher probabilities of using alcohol (0.93), and marijuana (0.95), tobacco products [cigarettes (0.95), e-cigarettes (0.87), cigarillos (0.86), hookah (0.74)], non-prescribed painkillers/sedatives (0.68), and other drugs (0.63) compared to other classes." This study also found correlates between older age, lower academic performance, higher sensation seeking, sexual orientation and gender-minority status and higher incidence of polysubstance use.

Several of these afore mentioned correlates are also noted in a systematic review of 17 studies from mostly the United States which used latent class analysis to describe risk factors of substance use for adolescents ages 10-19 that was released in 2015 in the journal of *Drug and Alcohol Dependence*.[xxv] The studies were focused on groups of youth of many different demographic categories that often did not represent a random sample population. This review most often found that there were 3 to 4 classes to describe substance use among youth. Resoundingly, the largest class consisted of youth who abstained from substances and the smallest class consisted of youth who used multiple substances together. The review of 17 studies validate the 2019 study previously mentioned which found that the polysubstance use group had risk factors of older age, lower academic performance, higher sensation seeking, and minorities of sexual orientation and gender identity.

New Mexico

According to New Mexico's 2019 Youth Risk and Resiliency Survey (YRRS) results, 5.9% of youth in New Mexico report using more than two substances, not including tobacco, sedatives, and tranquilizers, and 13.6% report using one substance, again not including tobacco, sedatives, and tranquilizers. This CDC-sponsored youth survey collects data once every two years as part of the CDC's national Youth Risk Behavior Surveillance Survey.

Risky Substance Combinations

The mechanisms of polysubstance-involved deaths are usually more complicated than single-substance-involved deaths. (Table 1) There are adulterated substances, individual health and mental health conditions, tolerance, and unique reactions to substances that influence individual episodes. While it is beneficial to understand both long-term and short-term risks associated with certain combinations of substances used in specific sequences through specific routes, it's important to keep in mind that substances are not used in vacuums within a controlled experiment.

Table 1 presents single substance classes, the substance's deadly effect, and possible acute or sudden cause of death that is related to that substance class. This table does not address fatal conditions that are a result of chronic, long-term substance use. The medical language in these charts is defined in Appendix B. Appendix C describes substances by chemical class and substance effect.

Table 1

Single Substance Classes and the Associated Possible Cause of Acute Death		
Single Substance Class	**Effect of Substance**	**Possibe Cause of Substance-Involved Acute Death**
Alcohol	CNS Depressant, Cardiotoxin	Cardiac arrythmia and respiratory depression
Opioid	CNS Depressant	Respiratory depression
Stimulant	Cardiac Overactivity	Acute cardiac dysfunction, hyperthermia, and stroke
Benzodiazepine	CNS Depressant	Respiratory depression

Due to the increased complexity, a Journal of Pain article in December of 2020 stated that distinguishing between opioid overdoses, "polysubstance-induced respiratory depression" (PIRD), and "polysubstance-overdose deaths" (POD) would challenge current obsolete diagnoses and treatment approaches to evolve.[xxvi]

Table 2 presents substance class combinations and the possible acute cause of death that is related to each combination.

Table 2

Polysubstance Combinations and the Associated Possible Cause of Acute Death	
Substance Combinations	**Possible Cause of Substance-Involved Acute Death**
Alcohol and benzodiazepines	Polysubstance-induced respiratory depression (PIRD)
Alcohol and stimulants	Acute cardiac dysfunction, hyperthermia, and stroke
Alcohol and opioids	PIRD
Benzodiazpines and opioids	PIRD
Opioids and stimulants	Acute cardiac dysfunction and/or PIRD, hyperthermia, and stroke
Alcohol, benzodiazepines, and opioids	PIRD

People who inject substances are at higher risk for fatal conditions such as sepsis, botulism, and hepatitis C. Chronic substance use is associated with fatal conditions such as liver disease, congestive heart failure, ischemia, hypoxia, and pneumonia.

New Mexico's Adult Polysubstance Death Data

In 2019, 66.14% of substance-involved deaths involved two or more substances. Of these substance-related deaths, 33.86% were due to single substances. Second most frequently, 30.73% involved two substances. Three substances were involved in 17.07% of the deaths. When two or more substances are involved in a death, a primary, secondary, and possibly a tertiary substance are identified. The primary substance is identified as the main attributable cause of death. A secondary substance is defined as being involved at toxic enough levels to contribute to death, and the tertiary substance is found at lesser toxicity levels than the secondary substance.

Graph 2 and Table 3 are based upon a 2021 presentation by the New Mexico Department of Health's analysis of the New Mexico Bureau of Vital Records and Health Statistics. The table and graph first display a primary substance, the substance that was most measurably attributed to acute death. The second column of Table 3 displays secondary substances that were most frequently found to be

the secondary cause of death, although the two are not necessarily always together and are listed for additional context of possible tertiary substance involvement. The third column of Table 3 then identifies the number of secondary substances most identified with the primary substance as the cause of death.

Methamphetamine was the most common substance involved in substance-related deaths in both 2018 and 2019. From 2015-2019, methamphetamine was most often observed as a single substance-involved death, with no other substances involved. Second most frequently, it was observed in combination with heroin (38.4%) or prescription opioids (18.6%). Anecdotally, the stimulating effects of methamphetamine are wrongly believed to help overcome the central nervous system (CNS) depressant effect of opioids and may be viewed as protective against opioid overdoses. Addressing this misguided belief may affect substance use behaviors.[xxvii]

An important consideration for polysubstance use measures is the question of whether to query by specific substance, such as heroin or fentanyl, or by the substance chemical class, such as opioids (Appendix C). For instance, somewhat contrary to the claim made in the paragraph above that methamphetamine was most frequently observed as a single substance involved death, methamphetamine and the whole opioid class, including heroin, non-fentanyl prescription opioids, and fentanyl are also most frequently observed in polysubstance-involved deaths. This distinction highlights some of the complexities of analyzing polysubstance use by specific substance or by drug class. Ultimately, both yield insightful pieces of information.

Heroin was the second most common substance involved in polysubstance-involved deaths in New Mexico in 2015-2019. Methamphetamine was found to be the most common secondary substance involved in heroin-related deaths. (Table 3) A single secondary substance was most often observed in heroin-involved deaths.

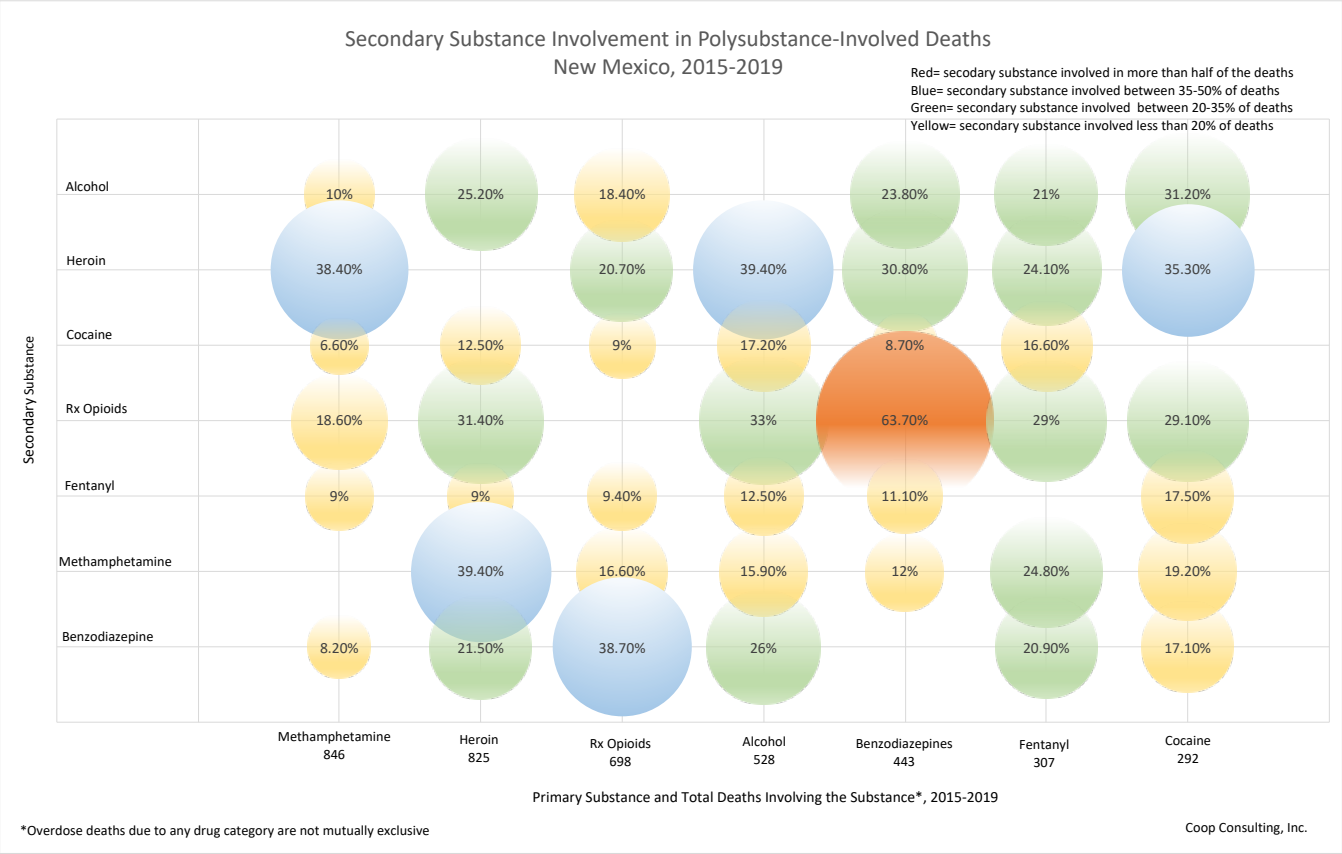
Table 3

New Mexican Polysubstance Death Combination Trends in 2019 (by decreasing prevalence)

Primary substance	Secondary substances in order of recorded observations (only the top two)	Number of other substances most observed in death
Methamphetamine	Heroin, Rx Opioids	0
Heroin	Meth, Rx Opioids	1
Non-Fentanyl Rx Opioids	Benzodiazepines, Heroin	1
Alcohol	Heroin, Rx Opioids	1
Benzodiazepines	Rx Opioids, Heroin	2
Fentanyl	Rx Opioids, Methamphetamine	1
Cocaine	Heroin, Alcohol	1

Source: New Mexico Bureau of Vital Records and Health Statistics

Graph 2: Bubble chart depicting polysubstance-involved deaths in New Mexico from 2015-2019



Source: NM DOH

Non-fentanyl prescription opioids were the third most prevalent substance-related cause of death. Most frequently, a secondary substance of benzodiazepines or heroin was involved. Non-fentanyl prescription opioid-related deaths most often involved one other substance. (Table 3)

Alcohol was the fourth most prevalent substance-related cause of death. Most frequently, a secondary substance of either heroin or prescription opioids was involved. Alcohol-related deaths usually involved one other substance. (Table 3)

Benzodiazepines as a class were the fifth most prevalent substance-related cause of death. Separately, alprazolam (Xanax) was involved nearly twice as often as diazepam (Valium). Most frequently, a secondary substance of prescription opioids or heroin were involved. Benzodiazepine-related deaths most often involved two other substances. (Table 3)

Fentanyl was the sixth most prevalent substance-related cause of death and is the most rapidly increasing. Most frequently, a secondary substance of prescription opioids or methamphetamine was

involved. Fentanyl-related deaths most often involved one other substance. (Table 3) Fentanyl has been increasingly found adulterating several other illicit substances in New Mexico and the western United States. Fentanyl testing strips are a valuable tool in helping users make decisions about the substances they use, as is sensory awareness of discerning fentanyl from other substances.

Cocaine was the seventh most prevalent substance-related cause of death. Most frequently, a secondary substance of heroin or alcohol was observed. Cocaine-related deaths most often involved one other substance. (Table 3)

Data Sources

Most of the publicly available data sources address single-substance questions, rather than polysubstance questions. Reliable data regarding polysubstance use comes from mortality data, self-reported surveys, and treatment data. Data about death is useful for deciding which substances or combinations of substances pose immediate risk of death to which people who use them. Self-reported surveys and treatment data are useful for understanding, correlating and predicting which groups of people are at risk for using certain substances before fatalities are identified.

The National Survey of Drug Use and Health (NSDUH) is a self-reported survey directed by SAMHSA that reports on single-substance use and mental health. The survey began in 1971 and expects a sample size of approximately 70,000 in 2021.

The Youth Risk Behavior Surveillance System (YRBSS) is a system of surveys directed by the Center for Disease Control and Prevention (CDC).[xxviii] The surveillance system collects information on six categories of health-related behaviors that contribute to the leading causes of death among youth and adults. Included are mutually exclusive measures of alcohol, tobacco, and other drug use. The New Mexico Department of Health collects a state-level local survey of middle and high school students, called the Youth Risk and Resiliency Survey (YRRS).[xxix] The YRRS includes some polysubstance use measurements.

The Behavioral Risk Factors Surveillance System (BRFSS) is a telephone survey system directed by the CDC. The survey began in 1984 and interviews more than 400,000 adults each year. The core national survey is used to gather information on health behaviors; however, the only questions about substance use are in regard to alcohol, tobacco, and cannabis.

Prescription Drug Monitoring Programs (PDMPs) are state directed databases that register schedule II-IV controlled substance prescriptions.[xxx] They are one of the best overdose prevention tools utilized by states, as prescribers and pharmacists are often required by state law to review and keep a

record of review of controlled prescriptions that patients fill prior to prescribing a controlled substance. Controlled prescriptions include benzodiazepines, opioids, and stimulants. PDMP's are useful for measuring concurrent prescriptions of controlled substances.

Treatment Episode Data Set (TEDS) is also directed by SAMHSA and began in 1992.[xxxi] It is a collection of treatment admissions and discharge data about individuals who sought treatment for substance use. The data includes demographics such as age, sex, ethnicity, race, and employment status. Also included is information about substance use, such as age first used, route of use, frequency of use, and preferences for primary, secondary, and tertiary substances.

New Mexico's Department of Health partners with the Office of Substance Abuse Prevention to produce annual Substance Abuse Epidemiological Profiles. The profile is a compilation of New Mexico's substance-related consequences (mortality), mental health, and consumption data for youth and adults. While most of the data in the profile has historically about single-substance use, there are some indicators reporting polysubstance use.

The New Mexico Department of Health is also the source for consequence or mortality data resulting from substance use, as collected by the New Mexico Bureau of Vital Records and Health Statistics. An analysis of single-substance mortality data is available through New Mexico's Indicator-Based Information System (NM-IBIS). At the time of preparing this white paper, New Mexico's polysubstance-involved death data is only available through data requests to New Mexico's Department of Health.

New Mexico's Office of Substance Abuse Prevention has partnered with the Pacific Institute Research Evaluation to conduct a state-wide survey since 2008, the New Mexico Community Survey (NMCS). The goal of the survey is to collect information about adult substance use and associated risky behaviors. In 2021, the NMCS will include questions about polysubstance use for the first time.

Because many of these national data collection surveys and reports are focused on single-substance issues, there is justification for state and local institutions to gather and analyze their own data to understand polysubstance use issues in their communities.

Appendix A:

Graph 3: Frequency of past month use of single substances by group of heroin users.

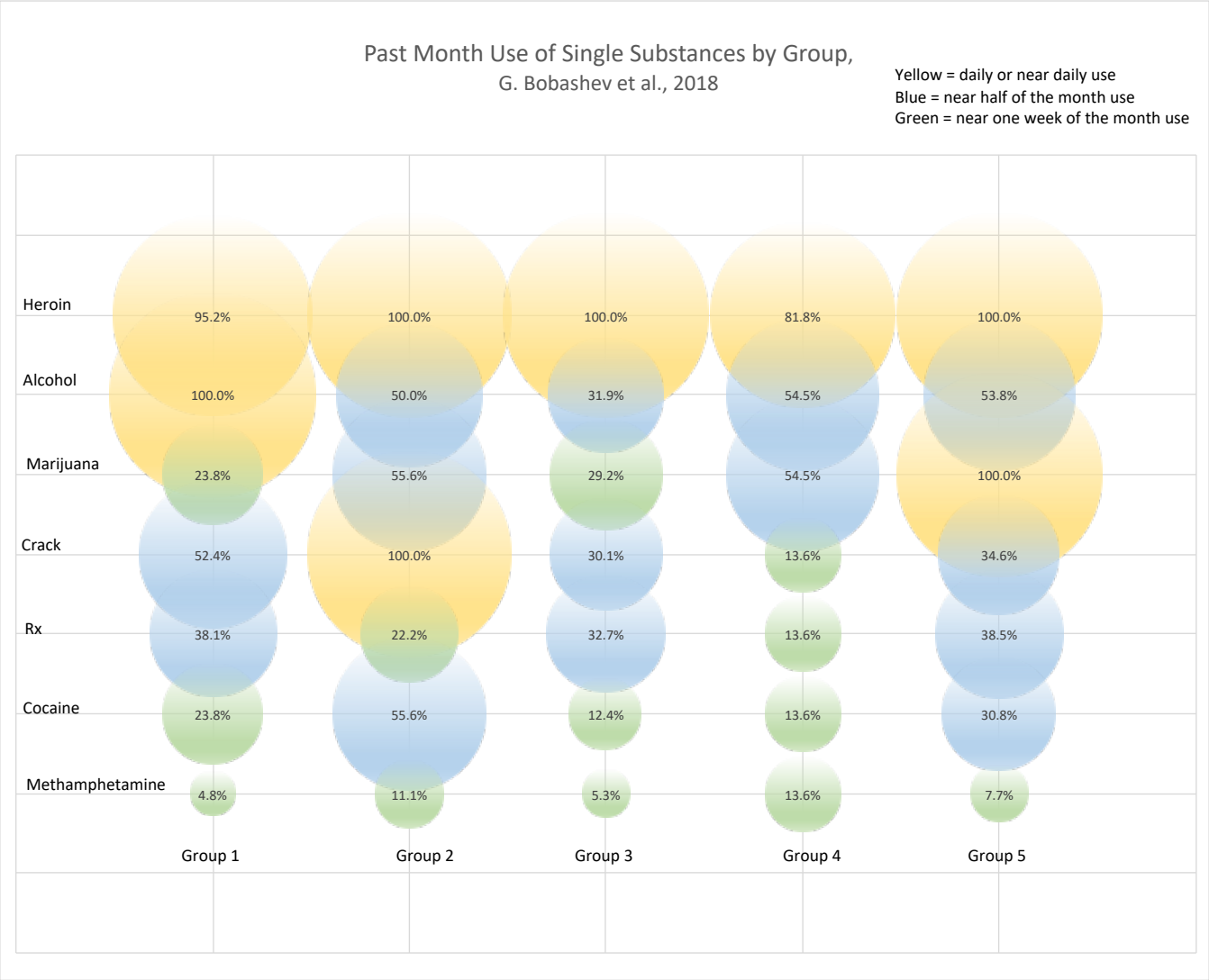


Image by Coop Consulting, Inc.

Graph 4: Past month use of two substances together by heroin user group

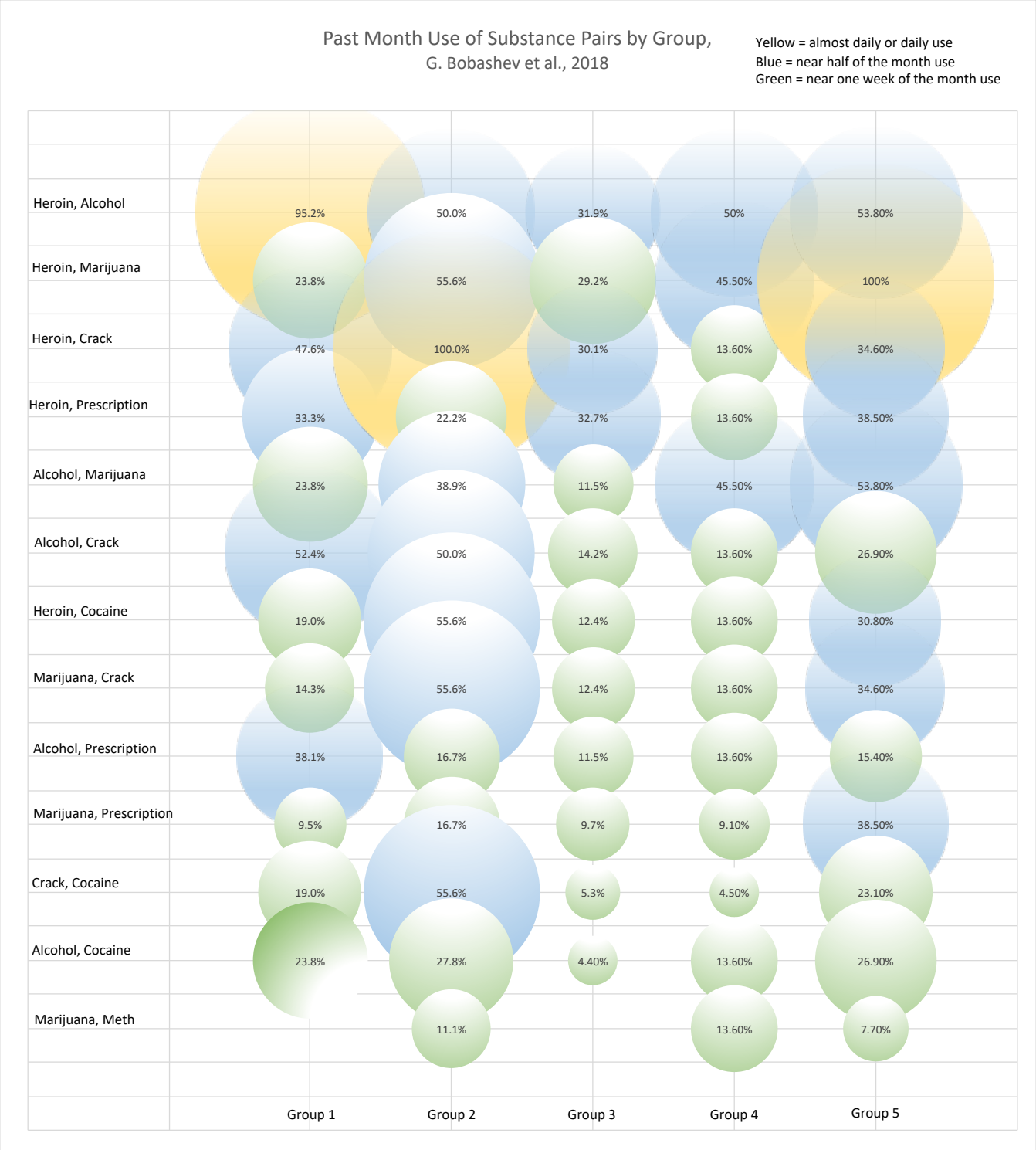
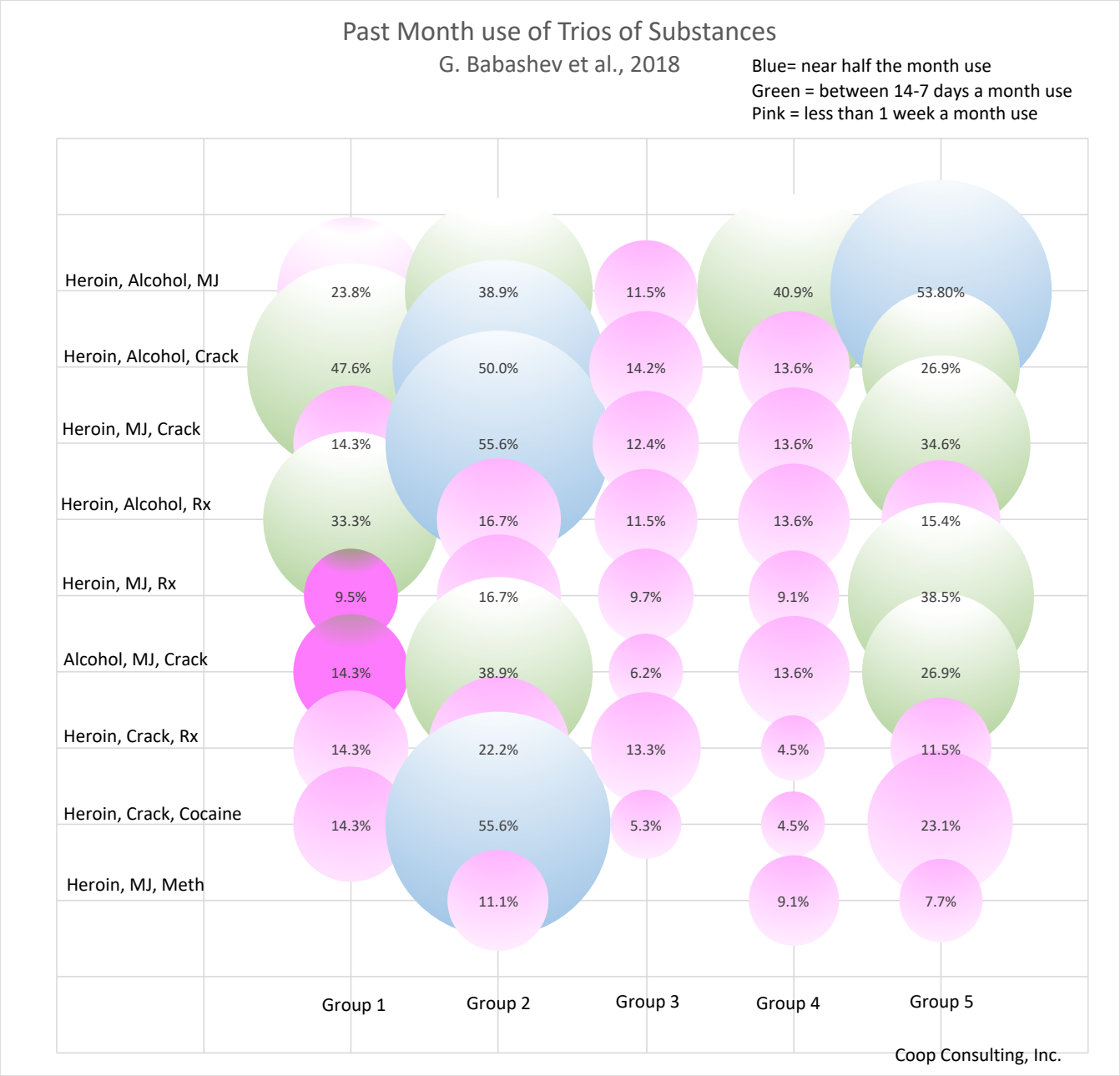


Image by Coop Consulting, Inc.

Graph 5: Past month use of three substances together by heroin user group



Appendix B: Medical Definitions

Acute cardiac dysfunction- a condition of suddenly worsening cardiac function

Acute- condition with sudden existence

Botulism- when the toxin from the *Clostridium botulinin* bacteria attacks the nervous system. Botulism can cause difficulty breathing and impair other important functions of the nervous system that support life.

Cardiac- pertaining to the heart

Cardiotoxicity- condition that results in heart muscle damage

Chronic- Condition that exists with longevity

CNS- Central Nervous System. Among many other components, the CNS contains the medulla, the part of the brain that regulates breathing.

Cortisol- Hormone that increases under stress, causing a fight or flight response, among other functions of metabolism and immune response

GABA- Gamma Aminobutyric Acid is a neurotransmitter that acts on the CNS, lowering heart and breathing rate, promoting relaxation.

Hyperthermia- overheating. In relationship to methamphetamine use, overheating can be a result of use of all metabolic resources, leading to multiple organ failure.

Hypoxia- absence of adequate oxygen to sustain organ or tissue function

Ischemia- inadequate blood supply to body tissues such as the heart or other organs and muscles

Respiratory depression - reduction in the drive to breath

Respiratory- pertaining to the body's ability to exchange oxygen for carbon dioxide through inhalation and exhalation

Sepsis- when bacteria from an infection enters the body's blood supply. Sepsis can cause multiple organ failure and death.

Schedule- A ranking of legal substances by potential for abuse. Schedule 1 substances have the highest potential for abuse and are not prescribed for medical use, while schedule 5 have relatively low potential for abuse.

Stroke- also known as a cerebrovascular accident (CVA) that results from an interrupted supply of blood to the brain. In relationship to methamphetamine, a stroke can be the result of acute cardiac dysfunction or cardiac overactivity

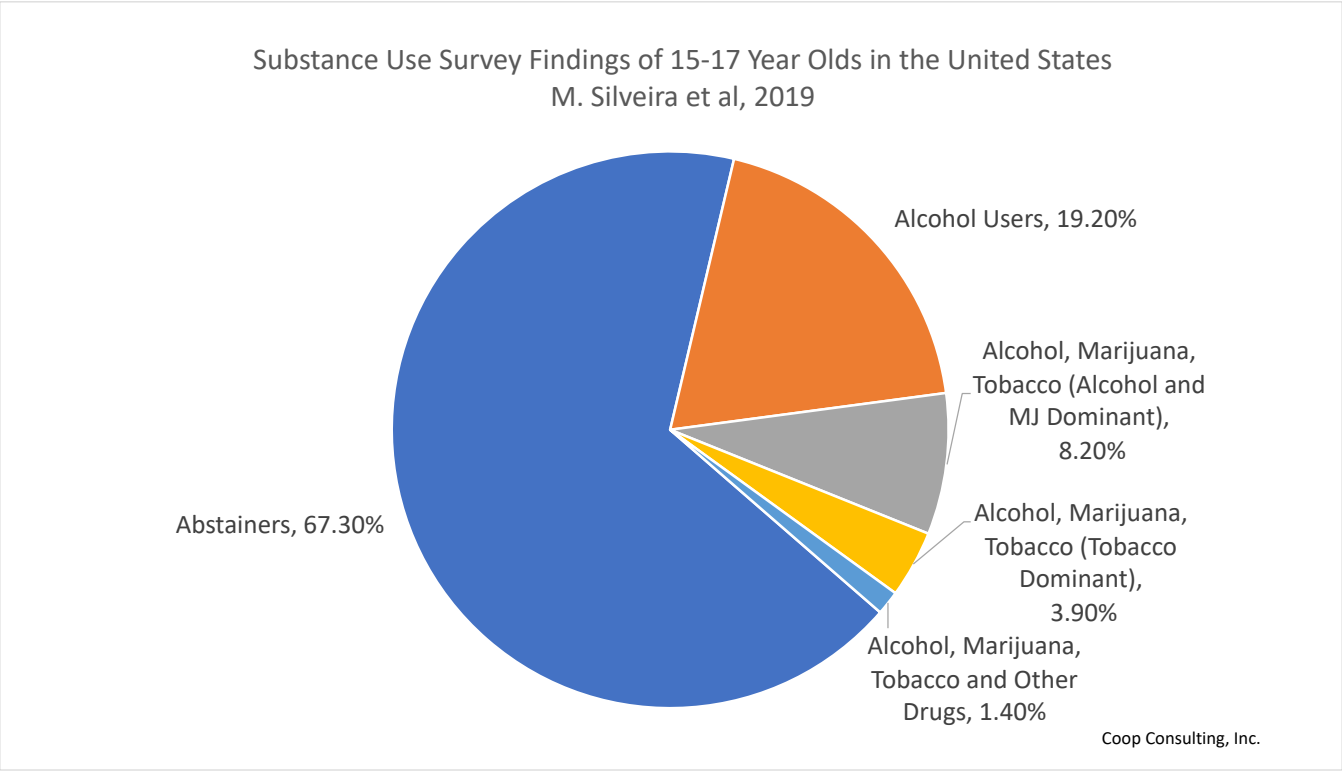
Substance class - substances are grouped by conditions medicines are prescribed to treat, the same mechanism of action, or by similar chemical configurations.

Appendix C: Substances

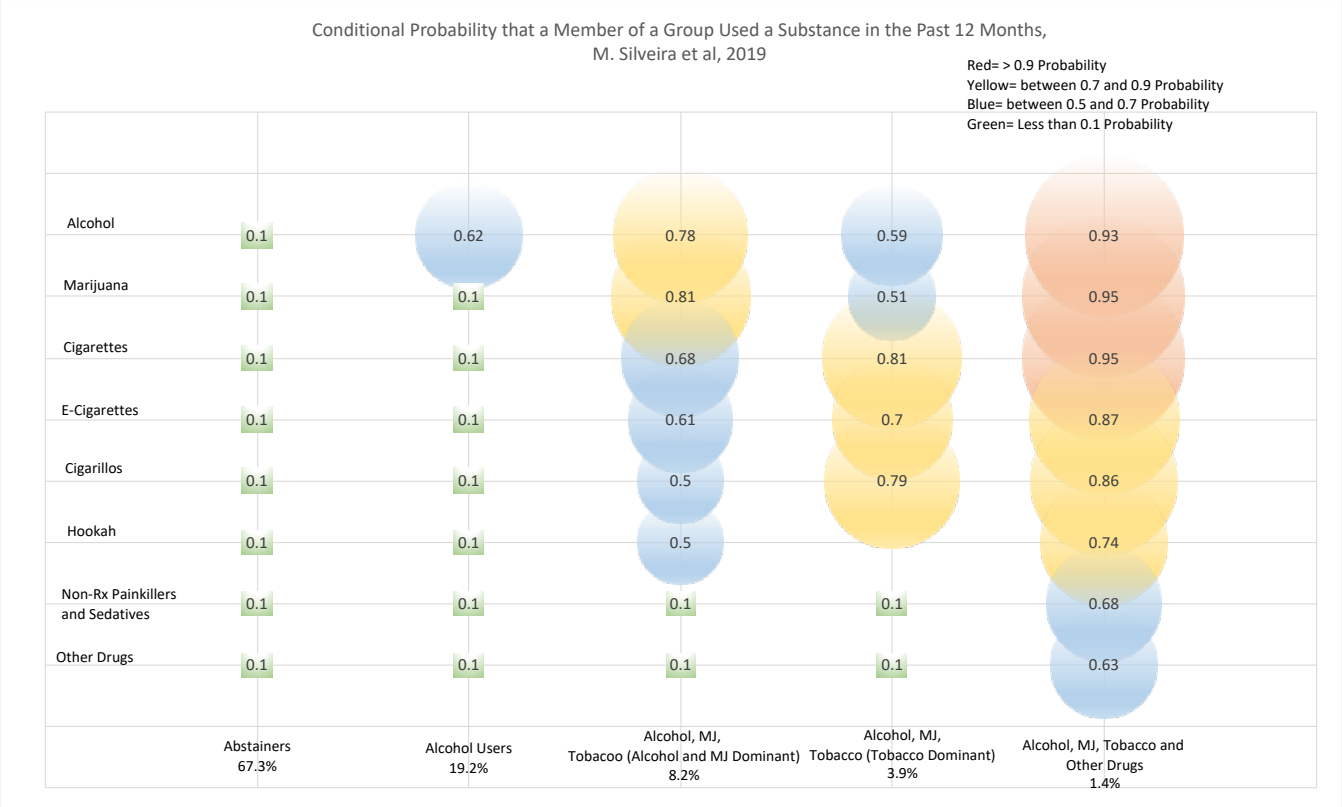
Substances by Chemical Class by Coop Consulting, Inc.		
Class	**Effect**	**Example Substance (not exhaustive)**
Barbiturates	Barbiturates are CNS depressants that share a similar mechanism of action as benzodiazepines, enhancing GABA's ability to bind to receptors for prolonged periods of time. This depresses the nervous system's activity through interrupting voltage signals. Due to their highly addictive properties, barbiturates are now mostly prescribed for epilepsy and are used in anesthesia.	Amytal; Luminal; Phenobarbital
Benzodiazepines	Enhances Gamma Aminobutyric Acid's (GABA) ability to bind to GABA receptors. Binding of GABA to the GABA receptor causes a decrease of CNS activity.	alprazolam (Xanax); diazepam (Valium); klonopin (Clonazepam); lorazepam (Ativan)
Cannabis	Cannabis acts on cannabinoid receptors on the brain. Individuals react differently to this, from hallucination, to elation, to drowsiness.	Marijuana; Hashish
Ethanol	Ethanol is best known as alcohol. It mimics GABA, and attaches to the GABA receptors. It does not increase GABA. By binding to the GABA receptor, alcohol suppresses nervous system activity. Alcohol is also a cardiotoxin.	Beer; Wine; Liquor
Opioids/Partial Opioid Agonists/Full Opioid Agonists	Opioids, partial opioid agonists, and full opioid agonists act on the opioid receptors of the brain and gut to reduce pain and nervous system activity.	Oxycodone; Opium; Morphine; Methadone; Hydromorphone; Suboxone; buprenorphine; heroin; fentanyl
Substances by Effect		
Stimulant	At low levels, stimulants activate the CNS, allowing for focus, energy, and alertness. At higher levels, stimulants produce paranoia, anger, and volatility.	Cocaine; Methamphetamine; Amphetamines and amphetamine derivatives; Adderall; Concerta; Dexedrine; Ritalin
Depressants/Sedative/Tranquilizer	Depressants, tranquilizers, and sedatives act on the central nervous system.	benzodiazepines; barbiturates ; alcohol; z-drugs; opioids
Hallucinogens	Hallucinogens alter consciousness, logic, and perceptions. Experiences vary from expanded consciousness, to seeing things that aren't there, to dissociative.	LSD; psilocybin; DMT
Inhalants	Mind-altering. Commonly found in household products that are stable at room temperature.	Spray paint; paint thinner; nail polish remover; gasoline
New Psychoactive Substances/Designer Drugs	Psychoactive, mind-altering, illicitly manufactured substances that differ slightly from licitly produced substances by chemical groups in a variety of drug categories	Synthetic cannabis; lab-produced ketamine

Appendix D: Patterns and covariates of polysubstance use in 15-17 year old youth according to Silveira's 2019 study.

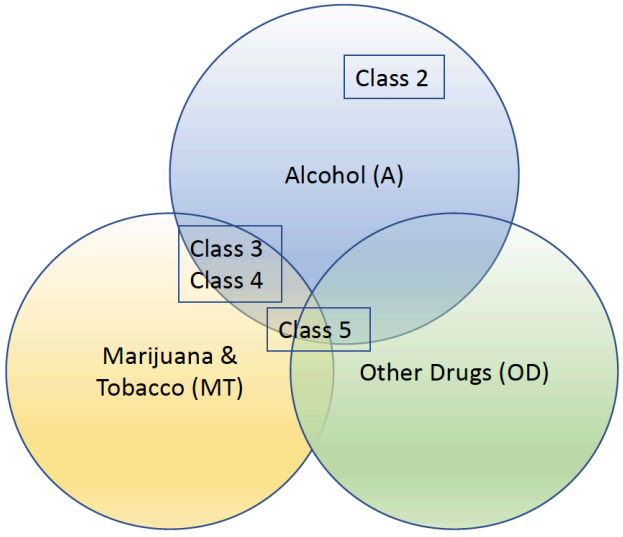
Graph 6:



Graph 7:



Graph 8:



Class 1= Abstainers (not pictured)
Class 2= Alcohol Users
Class 3= AMT users (AM Dominant)
Class 4= AMT users (T Dominant)
Class 5= AMTOD users

Source: M. Silveira et al, 2019

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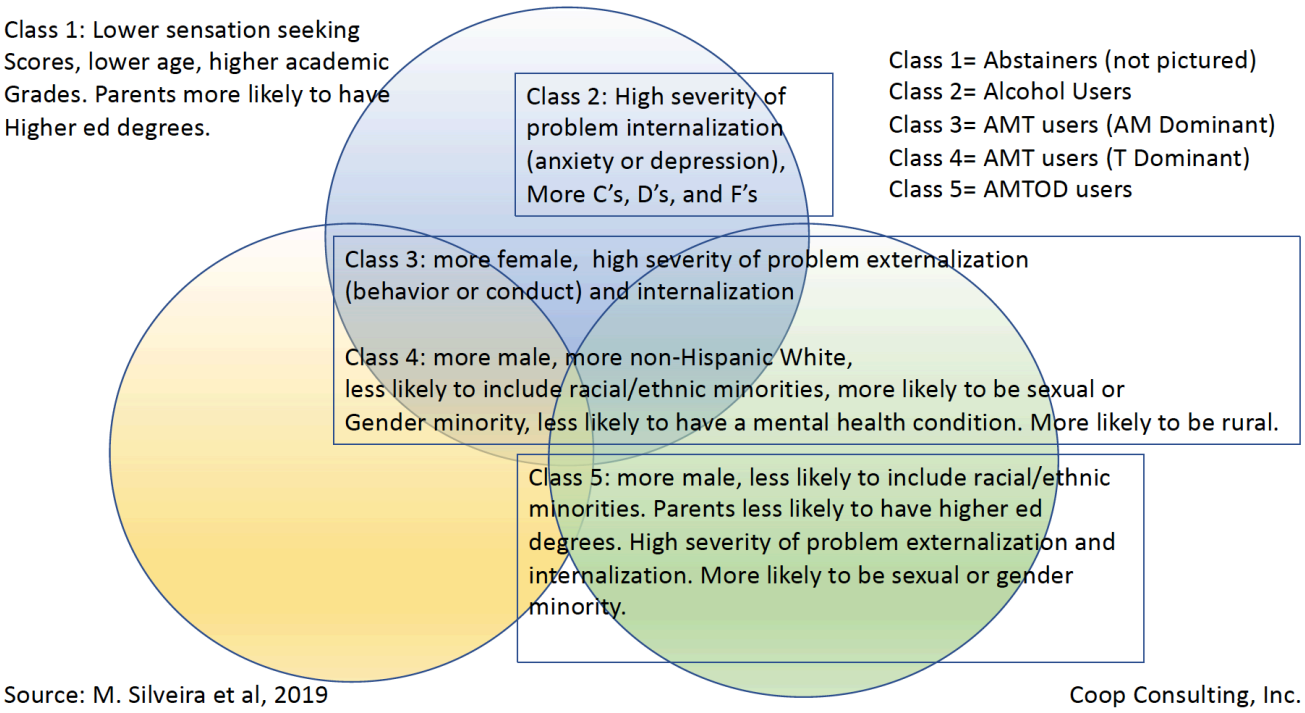
Graph 9:



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