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Patterns of Polysubstance Use Among Those with Tranquilizer or Sedative Misuse: Predictors and Functional Consequences

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Abstract

The misuse of tranquilizer and sedative medications (i.e., use without a prescription or at higher doses/longer periods of time than prescribed) is associated with myriad negative sequalae, such as suicidal behaviors and increased risk of overdose. Yet, prescription tranquilizer and sedative misuse has been largely overlooked by the scientific community, clinicians, and policymakers. We addressed this gap in the literature by characterizing subgroups of individuals with tranquilizer or sedative misuse, based on their patterns of polysubstance use. The present study analyzed data from two samples of individuals with past-month tranquilizer or sedative misuse: respondents of a nationally-representative household survey (general population sample; *N*=970) and individuals in substance use disorder treatment (clinical sample; *N*=451). Using latent class analysis, we identified two patterns of polysubstance use in the general population sample: (1) sedative misuse with low polysubstance use (approximately 16.6% of the sample), and (2) tranquilizer misuse with high polysubstance use (83.4%). Correlates of expected membership in the tranquilizer misuse with high polysubstance use class included younger age, more motives for misuse, and use without a prescription. We also identified two latent classes in the clinical sample: opioid use with high polysubstance

use (approximately 73.1% of the sample) and binge alcohol use with moderate polysubstance use (26.9%). Younger age and lower levels of anxiety sensitivity were associated with expected membership in the opioid use with high polysubstance use class. These results indicate that a majority of tranquilizer/sedative misuse does not occur in isolation, but, rather, is part of a pattern of polysubstance use. This finding is concerning, given the increased risk of overdose when tranquilizers and sedatives are combined with other substances.

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Introduction

Prescription tranquilizers and sedatives represent several classes of central nervous system depressants (e.g., benzodiazepines, barbiturates, z-drugs) that produce anxiolytic, hypnotic, and anticonvulsant effects (National Institute on Drug Abuse, 2011). Tranquilizers and sedatives, particularly benzodiazepines, are among the most commonly prescribed psychiatric medications in the United States (U.S.) (Lindsley, 2012; Moore & Mattison, 2017). In 2013, 13.5 million adults in the U.S. filled a benzodiazepine prescription, representing a 65% increase since 1996 (Bachhuber, Hennessy, Cunningham, & Starrels, 2016).

Although tranquilizers and sedatives are effective pharmacotherapies for anxiety (Starcevic, 2014), insomnia (Atkin, Comai, & Gobbi, 2018; Holbrook, Crowther, Lotter, & Endeshaw, 2001), and alcohol withdrawal (Amato, Minozzi, Vecchi, & Davoli, 2010), they also produce positive subjective effects and subsequent self-administration, known as abuse liability (de Wit & Griffiths, 1991; Griffiths & Johnson, 2005; J. D. Jones, Mogali, & Comer, 2012). Accordingly, tranquilizer or sedative misuse refers to use of these medications without a prescription, for longer periods of time or at higher doses than prescribed, or for reasons other than prescribed (e.g., to get high) (National Institute on Drug Abuse, 2018). Results from the National Survey on Drug Use and Health (NSDUH) indicate that 2.2% of U.S. citizens ages 12 and older misused tranquilizers (e.g., clonazepam, alprazolam, buspirone, cyclobenzaprine) in 2017, making tranquilizers the third most commonly misused illicit or prescription substance in the U.S. (Center for Behavioral Health Statistics and Quality, 2018). An additional 0.5% misused sedative medications (e.g., barbiturates, temazepam, triazolam) (Center for Behavioral Health

Statistics and Quality, 2018). As noted above, benzodiazepine prescriptions have increased over the past two decades; however, rates of tranquilizer and sedative misuse have remained relatively stable (Votaw, Geyer, Rieselbach, & McHugh, in press).

Estimating the prevalence of tranquilizer and sedative misuse in the U.S. is complicated by methodological features of population-based surveys that provide estimates of substance misuse and substance use disorders. Specifically, tranquilizers and sedatives represent different drug classes in these surveys, even though both include benzodiazepine products and have similar indications (e.g., insomnia, anxiety) (Center for Behavioral Health Statistics and Quality, 2017; Johnston et al., 2018). Accordingly, secondary data analyses of population-based data commonly combine these two classes (Becker, Fiellin, & Desai, 2007; Goodwin & Hasin, 2002), while analyses of clinical data have primarily examined benzodiazepine misuse, exclusively. Throughout this thesis, we will refer to the misuse of tranquilizers and sedatives, in combination, though many reviewed studies specifically examined benzodiazepine misuse.

Tranquilizer and Sedative Misuse: A Problem Unique to Polysubstance Users?

In the general population, polysubstance use (i.e., total number of substances used) and other substance use disorders increase the risk of tranquilizer and sedative misuse and dependence (Becker et al., 2007; Fenton, Keyes, Martins, & Hasin, 2010; Goodwin & Hasin, 2002; Huang et al., 2006). Accordingly, rates of tranquilizer and sedative misuse are much higher among those with other substance use disorders, as compared to the general population. Among those with opioid use disorder, approximately 50% of treatment-seekers (McHugh et al., 2017; Stein, Kanabar, Anderson, Lembke, & Bailey, 2016; Vogel et al., 2013) and over 20% of those in the

general population (Votaw, Witkiewitz, Valeri, Bogunovic, & McHugh, 2019) report past-month tranquilizer or sedative misuse. Limited available evidence among those with alcohol use disorder suggests that rates of past-month tranquilizer or sedative misuse are approximately 2.7% in the general population (Votaw et al., 2019) and 19% among treatment-seekers (McHugh, Geyer, Karakula, Griffin, & Weiss, 2018).

Even among those with substance use disorders, use of specific substances (e.g., marijuana, cocaine) and overall polysubstance use incrementally predict tranquilizer and sedative misuse. For example, several studies among those in opioid use disorder treatment indicate that cocaine use (Schuman-Olivier et al., 2013; Stein, Anderson, Kenney, & Bailey, 2017), amphetamine use (Lavie, Fatséas, Denis, & Auriacombe, 2009; Schuman-Olivier et al., 2013; Stein et al., 2017), marijuana use (Ghitza, Epstein, & Preston, 2008), and more total substances used (Lavie et al., 2009; Schuman-Olivier et al., 2013) are associated with increased risk of misuse. Polysubstance use has also been associated with misuse among those seeking treatment for alcohol use disorder (McHugh et al., 2018). In a recent analysis of NSDUH data, each additional substance used in the past year was associated with 1.4 greater odds of past-month tranquilizer or sedative misuse among those with opioid use disorder, 2.3 greater odds among those with alcohol use disorder, and 1.5 greater odds among those with co-occurring opioid and alcohol use disorders (Votaw et al., 2019).

The high prevalence of tranquilizer and sedative misuse among those with substance use disorders might be partly explained by a greater number of motives, or reasons, for misuse in these populations. Tranquilizers and sedatives are most commonly misused to reduce negative affective (e.g., anxiety) and somatic (e.g., insomnia) states

(Votaw et al., in press). However, individuals with opioid use disorder report additional motives for tranquilizer and sedative misuse, including use to get high, to cope with withdrawal, and to modify the effects of other substances (e.g., increasing effects of opioids, decreasing effects of stimulants) (Gelkopf, Bleich, Hayward, Bodner, & Adelson, 1999; Mateu-Gelabert et al., 2017; Vogel et al., 2013). Thus, several features of chronic substance use (e.g., high levels of negative affective and somatic symptoms, decreased reward sensitivity; Koob & Le Moal, 2008), might motivate those with substance use disorders to misuse tranquilizers and sedatives for myriad reasons, thus increasing the overall prevalence of misuse.

Predictors of Tranquilizer and Sedative Misuse

These reviewed findings raise the following questions: does tranquilizer and sedative misuse occur independent of polysubstance use? If so, what motivates the misuse of tranquilizers and sedatives among individuals without polysubstance use? Several population-based studies have identified factors that are uniquely associated with risk of tranquilizer and sedative misuse, even when controlling for other substance use and substance use disorders. Sociodemographic factors consistently associated with misuse include younger age (i.e., ages 18-25) and non-Hispanic white racial/ethnic identity (Votaw et al., in press). Although several large, population-based studies indicate that female gender is associated with tranquilizer and sedative misuse, males typically have higher risk of misuse when controlling for receipt of a tranquilizer/sedative prescription (Votaw et al., in press). Females and non-Hispanic white individuals are more likely to receive a benzodiazepine prescription (Olfson, King, & Schoenbaum, 2015), which might increase risk of misuse due to greater availability and/or psychiatric

severity. Indeed, receipt of a tranquilizer or sedative prescription is associated with 1.9 greater odds of misuse and 2.6 greater odds of a use disorder, even when controlling for lifetime anxiety disorder diagnoses (Fenton et al., 2010).

Numerous general population studies have identified associations between psychiatric distress (e.g., psychiatric disorders, general distress) and tranquilizer/sedative misuse and use disorder (Votaw et al., in press). Among those with opioid use disorder, symptoms of anxiety and depression and affective vulnerabilities have been consistently associated with tranquilizer or sedative misuse (Eiroa-Orosa et al., 2010; McHugh et al., 2017; Stein et al., 2017). Anxiety sensitivity—a trait-like vulnerability characterized by the fear of anxiety symptoms and sensations—has been associated with regular tranquilizer or sedative misuse (Hearon et al., 2011), greater frequency of misuse (McHugh et al., 2017), and dependence (Conrod, Pihl, Stewart, & Dongier, 2000). These findings have been recently replicated among those with alcohol use disorder (McHugh et al., 2018).

There is also evidence for associations between physical health issues and tranquilizer/sedative misuse among the general population, those with opioid use disorder, and other subgroups, such as healthcare workers and adolescents presenting to the emergency department (Votaw et al., in press). However, measures of physical health examined have varied widely, including self-reported general health, pain severity, sleep dysfunction, and disability status.

Functional Consequences Associated with Tranquilizer and Sedative Misuse

Given high rates of tranquilizer and sedative misuse among those with opioid use disorder (see above), studies examining functional consequences associated with misuse

have primarily enrolled individuals with opioid use disorder and/or those with injection drug use. Accordingly, most functional consequences associated with tranquilizer and sedative misuse are particularly relevant to individuals with substance use disorders, such as overdose, HIV/HCV infection, treatment attrition, and opioid relapse. Unless otherwise specified, the literature reviewed below will focus on functional consequences associated with tranquilizer and sedative misuse among those with opioid use disorder and/or injection drug use.

The most consistent—and most concerning—consequence associated with misuse is the increased risk of heart rate and respiratory depression when tranquilizers and sedatives, particularly benzodiazepines, are combined with opioids and/or alcohol (Gudin, Mogali, Jones, & Comer, 2013). Overdose deaths involving benzodiazepines (often in combination with other substances) have increased more than 300% from 2002-2015 (National Institute on Drug Abuse, 2017). Among individuals with opioid misuse and opioid use disorder, tranquilizer and sedative misuse and dependence have been retrospectively (Galea et al., 2006; Hakansson, Schlyter, & Berglund, 2008; Kerr et al., 2007; Maloney, Degenhardt, Darke, & Nelson, 2009; Wines Jr., Saitz, Horton, Lloyd-Travaglini, & Samet, 2007) and prospectively (Gossop, Stewart, Treacy, & Marsden, 2002) associated with opioid overdose. Beyond increasing risk of overdose, those with tranquilizer or sedative misuse have elevated rates of HIV (Ickowicz et al., 2015) and Hepatitis C (Bleich et al., 1999) infection, as well as other sexually transmitted infections (S Darke, Hall, Ross, & Wodak, 1992). Misuse is also associated with a history of attempted suicide among several populations, including those in the general population (Borges, Walters, & Kessler, 2000), adolescents (Kokkevi et al., 2012), those with

alcohol dependence, (Preuss et al., 2003) and those with opioid use disorder and/or injection drug use (Artenie, Bruneau, Roy, et al., 2015; Artenie, Bruneau, Zang, et al., 2015; Shane Darke, Ross, Lynskey, & Teesson, 2004; Wines, Saitz, Horton, Lloyd-Travaglini, & Samet, 2004). Accordingly, tranquilizer and sedative misuse and dependence are associated with overall mortality among those with opioid use disorder (Pavarin, 2015; Peles, Schreiber, & Adelson, 2010).

In addition, misuse of tranquilizer and sedative medications is associated with a number of behavioral consequences among those with opioid misuse. Those with misuse are more likely to report more frequent injection drug use, unsafe injection behaviors (e.g., sharing injection equipment), and risky sexual practices (e.g., unsafe sex, prostitution) (Darke et al., 1992; Darke, Swift, Hall, & Ross, 1993; Tucker et al., 2016), which might explain the associations between tranquilizer/sedative misuse and infectious disease. Misuse is also associated with increased risk of criminal involvement, particularly property crime and selling drugs (Comiskey, Stapleton, & Kelly, 2012; Shane Darke et al., 2010; Horyniak et al., 2016). Several studies indicate that misuse is associated with opioid use disorder treatment attrition (Eiroa-Orosa et al., 2010; Peles et al., 2010; Schiff, Levit, & Moreno, 2007; White et al., 2014) and continued substance use throughout treatment (Brandt, Taverna, & Hallock, 2014; Shane Darke et al., 2010; Naji et al., 2016), though other studies have not identified an effect of misuse on opioid use disorder treatment outcomes (Proctor et al., 2015; Schuman-Olivier et al., 2013).

Despite relatively consistent associations between tranquilizer and sedative misuse and poor outcomes, explanations for these associations are unclear. Some authors have posited that tranquilizer and sedative misuse might increase risk of functional

consequences by acute decreases in inhibition (Artenie, Bruneau, Roy, et al., 2015; Artenie, Bruneau, Zang, et al., 2015; S Darke et al., 1992; Wines et al., 2004), while others have suggested that those with tranquilizer or sedative misuse might have greater psychiatric severity (both as an antecedent and consequences of tranquilizer or sedative misuse), which is associated with poorer outcomes (Artenie, Bruneau, Roy, et al., 2015; Artenie, Bruneau, Zang, et al., 2015; Naji et al., 2016; Wines et al., 2004). It is also plausible that greater substance use involvement among those with tranquilizer or sedative misuse could explain the associations between misuse and poor functional outcomes, but this hypothesis has not been systematically investigated. Notably, only one of the previously reviewed studies controlled for level of polysubstance use (Darke et al., 2010), despite evidence that polysubstance use was also associated with negative outcomes in several of the studies (Darke et al., 2004; Gossop et al., 2002; Wines et al., 2004; Wines Jr. et al., 2007). Another previous study found that tranquilizer/sedative misuse was associated with recent injection drug use in bivariate analyses, but this effect was mitigated when controlling for polysubstance use (as well as other factors that were significant in bivariate analyses, including female gender, having a sexual partner who injected drugs, and poorer general health) (Darke, Swift, Hall, & Ross, 1994). Thus, the associations between tranquilizer and sedative misuse and functional consequences might be explained by greater levels of substance use involvement.

Current Studies

Most studies characterizing tranquilizer and sedative misuse have enrolled samples with severe substance use presentations, particularly those with opioid use disorder (Bouvier et al., 2017; Ghitza et al., 2008; Lavie et al., 2009; McHugh et al.,

2017; Schuman-Olivier et al., 2013; Stein et al., 2017, 2016; Vogel et al., 2013). Although there is robust evidence to suggest that those with polysubstance use are the most vulnerable to tranquilizer and sedative misuse (Becker et al., 2007; Fenton et al., 2010; Goodwin & Hasin, 2002; Huang et al., 2006; Votaw et al., 2019), it is unclear whether misuse occurs in isolation. The present study aimed to address this gap by using latent class analysis (LCA) to identify patterns of polysubstance use among those with past-month tranquilizer or sedative misuse. LCA is a form of mixture modeling that uses a person-centered approach to detect heterogeneity in a population (Nylund, 2007). Utilizing latent class analysis provides an opportunity to examine distinct patterns of polysubstance use among a larger population of those with current tranquilizer or sedative misuse, including determining the presence (or lack thereof) of individuals with low levels of polysubstance use.

The second aim of the study was to examine sociodemographic, clinical (e.g., measures of psychiatric distress), and substance use (e.g., motives for tranquilizer/sedative misuse) correlates of identified latent classes. This aim was accomplished through the use of multinomial logistic regression models, using a model-based approach. Examining correlates of identified classes allowed for the identification of potential risk factors for more severe polysubstance use. Characterizing those with lower levels of polysubstance use helped to determine populations who have been overlooked in studies examining the etiology of tranquilizer and sedative misuse, who may be important targets for future research.

Lastly, we examined functional consequences associated with identified latent classes using distal outcome analysis. Distal outcome analysis estimates the proportion of

individuals in a latent class who will experience a particular outcome. A number of consequences have been consistently associated with tranquilizer and sedative misuse, including risk of overdose (Galea et al., 2006; Hakansson et al., 2008; Kerr et al., 2007; Maloney et al., 2009; Wines Jr. et al., 2007), infectious disease (Bleich et al., 1999; S Darke et al., 1992; Ickowicz et al., 2015), risky sexual behavior/risky injection practices (S Darke et al., 1992, 1993; Tucker et al., 2016), increased criminal involvement (Comiskey et al., 2012; Shane Darke et al., 2010; Horyniak et al., 2016), suicidal ideation/attempt (Artenie, Bruneau, Roy, et al., 2015; Artenie, Bruneau, Zang, et al., 2015; Shane Darke et al., 2004; Wines et al., 2004), and poor substance use disorder treatment outcomes (Brandt et al., 2014; Shane Darke et al., 2010; Naji et al., 2016). Authors of these studies have posited that these associations are due to the inhibitory effects of tranquilizers and sedatives, increased psychiatric distress and functional severity among those with tranquilizer or sedative misuse, or both (Artenie, Bruneau, Roy, et al., 2015; Artenie, Bruneau, Zang, et al., 2015; Naji et al., 2016; Wines et al., 2004). No studies to date have suggested or examined the possibility that these associations are due to increases in overall polysubstance use among those with misuse. Examining functional consequences as a function of polysubstance use involvement evaluated initial evidence for this hypothesis.

Importantly, we executed these aims in two studies enrolling distinct samples: (1) respondents of a population-based household survey (i.e., general population sample) and (2) individuals in inpatient detoxification treatment for substance use disorders (i.e., clinical sample). The general population sample allowed for the potential to detect a subgroup(s) with lower levels of polysubstance use. However, if we utilized this sample

alone, those with more severe substance use presentations might have been identified as one (or multiple) homogenous group(s). Thus, we also utilized a clinical sample to detect further heterogeneity among those with severe substance use presentations. Characterizing patterns of polysubstance use among a clinical sample with substance use disorders is important, given that this population displays high rates of tranquilizer and sedative misuse and the consequences associated with misuse.

Hypotheses

First, we hypothesized that we would identify distinct patterns of polysubstance use among those with tranquilizer or sedative misuse. Among the general population sample, we hypothesized that identified latent classes would be interpreted as: (1) low levels of polysubstance use, (2) alcohol/marijuana use, and (3) high levels of polysubstance use. These hypotheses were informed by a previous study that utilized LCA to identify patterns of polysubstance use among a general population sample of individuals with prescription amphetamine misuse (Chen et al., 2014). The most common latent class in this analysis was the low polysubstance use class, consisting of approximately 53.3% of the sample. However, we hypothesized that the high polysubstance use class would be the most prevalent in our sample, given robust associations between polysubstance use and tranquilizer/sedative misuse. Among the clinical sample, given that nearly all participants have either alcohol or opioid use disorder, we hypothesized that identified latent classes will be interpreted as: (1) concurrent alcohol use, (2) concurrent opioid use, and (3) high levels of polysubstance use.

Second, we hypothesized that the identified latent classes would display distinct sociodemographic and substance use characteristics. For example, we hypothesized that female gender, older age, and minority racial/ethnic status would be associated with the class(es) characterized by lower levels of polysubstance use, while male gender, younger age, white race, and greater psychiatric and physical distress would be associated with higher levels of polysubstance use. We also expected that a greater number of reasons, or motives, for tranquilizer/sedative misuse would be associated with greater levels of polysubstance use, as would use without a prescription. Finally, we hypothesized that individuals with expected classification in the polysubstance use class(es) would display the highest proportions of functional consequences, such as criminality, suicidal behaviors, and sexually transmitted infections.

Study 1: General Population Sample

Method

Data source and participants. This study entailed a secondary data analysis of National Survey on Drug Use and Health (NSDUH) respondents. The NSDUH is an annual, population-based survey of U.S. citizens ages 12 and older. The purpose of the NSDUH is to identify nationwide prevalence rates for substance use misuse and substance use disorders. Households with potential respondents are identified through an independent, multistage probability sample within the 50 states and Washington D.C. In order to protect participant confidentiality, a de-identified subset of the total annual sample is available for public use. Detailed NSDUH methodology has been previously reported (Center for Behavioral Health Statistics and Quality, 2017).

The present study utilized combined data from the 2015 and 2016 public use data files. Participants for the present analysis were adult respondents who reported the misuse of tranquilizer or sedative medications in the previous month (*N*=988).

Measures.

Sociodemographics. The following sociodemographic measures were included in the present analysis: gender, age (categorized as 18-25 years old, 26-34, 35 and older), and racial/ethnic identity (non-Hispanic White vs. racial/ethnic minority).

Substance use. To determine lifetime prescription tranquilizer (e.g., alprazolam, lorazepam, diazepam, buspirone) or sedative (e.g., barbiturates, temapzepam, triazolam, zolpidem) use, participants were shown cards with pictures and names of these medications and specified which, if any, they had ever used. Participants with lifetime tranquilizer or sedative use indicated if they had ever misused these medications, which was defined as use at higher doses/more frequently than prescribed, for reasons other than prescribed, or use without a prescription. Those with lifetime tranquilizer or sedative misuse then indicated the length of time since their last episode of misuse. The frequency of past-year and past-month tranquilizer and sedative misuse was also assessed. Those with past-month tranquilizer or sedative misuse were included in the present analysis. We decided to include those with past-month tranquilizer *or* sedative misuse, given that both classes include benzodiazepine products and are prescribed for similar indications (e.g., sleep, anxiety). Combining these classes is consistent with previous analyses of NSDUH data (Becker et al., 2007; Goodwin & Hasin, 2002).

Similar procedures as described above were used to determine past-month prescription opioid and amphetamine misuse. Participants were also asked if they had

ever used any illicit substances (e.g., marijuana, cocaine/crack cocaine, methamphetamine, heroin, hallucinogens, inhalants) or alcohol. Binge alcohol use (4/5+ drinks for men/women, respectively) was also assessed. Participants with lifetime use of illicit drugs or alcohol answered a standardized set of questions to determine length of time since their most recent use and frequency of use. The present analysis utilized data on past-month use (yes/no) of a range of substances (e.g., prescription amphetamines, prescription opioids, marijuana, cocaine, heroin, binge alcohol use). Measures of past-month frequency of use were also utilized and were recoded into categorical measures of frequency (0, 1–3, 4–8, 9–15, or 16–30 days), which were informed by the Brief Addiction Monitor (Cacciola et al., 2013).

Misuse behaviors and motives. Those with past-year tranquilizer or sedative misuse reported their behaviors that comprised misuse for both tranquilizers and sedatives, separately. Specifically, participants were asked: "Which of these statements describe your use of tranquilizers/sedatives at any time in the past 12 months?" Response options included the following: used without my own prescription in the past 12 months, used in greater amounts than prescribed in the past 12 months, used more often than prescribed in the past 12 months, used over longer periods of time than prescribed in the past 12 months, and used in some other way that was not directed by a physician in the past 12 months. Participants were able to choose more than one response. Any misuse of tranquilizer or sedative medications without a prescription in the past year (termed nonmedical use) vs. misusing one's own prescription for longer periods of time, at higher doses, or for longer periods of time than prescribed (termed medical misuse), was included as a dichotomous variable in the present analysis.

To determine motives, or reasons, for tranquilizer and sedative misuse, participants were asked: "Now think about the last time you used tranquilizers/sedatives in any way a doctor did not direct you to. What were the reasons you used tranquilizers/sedatives the last time?" Notably, this question only referred to the participants' *last* episode of misuse. Response options included the following: to relax/relieve tension, to experiment/to see what tranquilizers/sedatives are like, to feel good/get high, to help with sleep, to help me with feelings/emotions, to increase/decrease the effect(s) of some other drug, because I'm hooked/have to have sedatives, and some other reason. Participants were able to choose more than one response and they reported motives for tranquilizer and sedative misuse separately. Participants' total number of motives at their last episode of misuse was included in the present analysis. For those with both tranquilizer and sedative misuse, motives were totaled for their last misuse of tranquilizers, as opposed to sedatives, given that a majority of the sample reported tranquilizer misuse in the previous month.

Mental health. The measure of psychiatric distress utilized was the Kessler Psychological Distress Scale (K6 Scale) (Kessler et al., 2003). Notably, this scale is only administered to participants over the age of 18, which limited our analysis to adult respondents. The Kessler K6 scale is a nonspecific measure of psychiatric distress that includes 6 questions about the frequency of mood and anxiety symptoms. Specifically, participants were asked to answer the following questions pertaining to the previous month: "How often did you feel nervous?", "How often did you feel hopeless?", "How often did you feel restless or fidgety?", "How often did you feel so sad or depressed that nothing could cheer you up?", "how often did you feel that everything was an effort?",

and "how often did you feel down on yourself, no good, or worthless?" Response options ranged from "none of the time" to "all of the time," representing a potential range of scores from 0 to 24. Higher scores indicate greater psychiatric distress in the previous month. The K6 scale has demonstrated satisfactory internal consistency reliability (Cronbach's α=0.89) and construct validity, as evidenced by the ability to differentiate those with and without serious mental illness (Kessler et al., 2003).

Functional consequences. Functional consequences were selected based on prior evidence of association with tranquilizer and sedative misuse (Votaw et al., in press) and included: past-year deviant behavior, past-year arrest, past-year suicidal ideation, past-year injection drug use, and past-year sexually transmitted infection (STI).

Consistent with previous analyses using NSDUH data (Chen et al., 2014; Hedden et al., 2010), past-year deviant behavior was determined by responses to the following questions: "During the past 12 months, how many times have you attacked someone with the intent to seriously hurt them?", "During the past 12 months, how many times have you sold illegal drugs", and "During the past 12 months, how many times have you stolen or tried to steal anything worth more than US $50?" Participants who reported any of these behaviors greater than one time were classified has having a past-year deviant behavior.

Past-year arrest status was determined by a question that asked participants "Not counting minor traffic violations, how many times during the past 12 months have you been arrested and booked for breaking a law?" Participants who were arrested at least once in the previous year were categorized as having a past-year arrest.

Past-year suicidal ideation was determined by an affirmative response to the following question: "At any time in the past 12 months, did you seriously think about trying to kill yourself?"

To determine past-year injection drug use, participants answered a question that asked if they had ever used a needle to inject any drug. Those with lifetime injection drug use indicated the amount of time since their last injection drug use.

Finally, STI status was determined by participants' responses to the following questions: "During the past 12 months, did you have a sexually transmitted disease such as chlamydia, gonorrhea, herpes or syphilis?" Participants were told to base their response on conversations they've had with their doctor.

Statistical analyses. First, latent class analysis (LCA) was utilized to identify patterns of polysubstance use in the previous month. LCA is a person-centered approach used to identify distinct subpopulations of individuals, based on similar responses to indicator variables. LCA estimates two parameters: (1) probabilities of endorsing the indicators, given latent class membership (i.e., item response probabilities), and (2) the prevalence of each class in the population (i.e., class probability) (Nylund, 2007).

Indicators for the current analysis were past-month misuse of prescription medications (e.g., prescription amphetamines, prescription opioids), illicit drugs (e.g., marijuana, cocaine, heroin, etc.), and binge alcohol use. Substances that were endorsed by <5% of the sample were combined with other substances of the same class (e.g., combining prescription amphetamine and methamphetamine use) or were excluded from analyses. The LCA was first estimated with a 1-class solution and increasing number of classes were estimated until the optimal model was identified. Model fit was assessed

using the Bayesian Information Criteria (BIC), where a lower BIC indicates a better fitting model, and the sample size adjusted Bayesian Information Criteria (aBIC), which adds a penalty for increasing parameters related to sample size. The optimal number of classes was identified by the lowest BIC (or the greatest rate of decrease in BIC) and aBIC and theoretical interpretability. Notably, we did not report the Lo-Mendell-Rubin adjusted likelihood ratio test (LRT) as an indicator of model fit given that LRT estimates do not account for complex sampling designs, such as those used by the NSDUH (see below for details on variables accounting for complex sampling designs; Muthén, 2016). Model entropy, a measurement of classification precision, was also interpreted and reported, with entropy greater than .80 indicating good classification precision.

All models were estimated with three different combinations of indictors and were evaluated for theoretical interpretability. First, indicators for the latent class analysis were included as binary (yes/no) past-month use of alcohol and illicit/prescription substances (LCA iteration 1). Second, for substances that were used by a high proportion of the sample in the previous month (i.e., >20%), categorical frequency indicators were utilized (LCA iteration 2). Lastly, a frequency indicator for past-month tranquilizer misuse and a binary indicator for past-month sedative misuse were added to the model (LCA iteration 3).

Potential predictors of latent class membership were included as covariates in the LCA with latent class membership as a categorical outcome variable. Predictors were factors that have previously demonstrated associations with the incidence and severity of tranquilizer and sedative misuse (Votaw et al., in press), and included: age (18-25, 26-34, 35+), gender, race/ethnicity (non-Hispanic white vs. racial/ethnic minority), total number

of motives for participants' last misuse of tranquilizers or sedatives, misuse behaviors (nonmedical use vs. medical misuse), and total K6 score in the previous month. Effect sizes reported are adjusted odds ratios (aOR), controlling for all covariates in the model.

Finally, distal outcome analysis was utilized to determine functional consequences associated with latent class membership, using the BCH approach (Asparouhov & Muthén, 2014). The BCH approach weights observations inversely to their classification error, or uncertainty. Thus, results were interpreted as the proportions of individuals within each identified latent class who were expected to experience the distal outcome, after weighting for classification error. Weighted Chi-square analyses were utilized to identify statistically significant differences in the proportion of distal outcomes across identified latent classes. The distal outcomes in the present analysis were functional consequences that have previously been associated with tranquilizer and sedative misuse (Votaw et al., in press), including the following: past-year deviant behavior, past-year arrest, past-year suicidal behavior, past-year injection drug use, and past-year STI.

SPSS version 25 was used to prepare data and compute descriptive statistics; all other analyses were conducted in M*Plus* version 8 (L. Muthén & Muthén, 2017). Descriptive statistics represent unweighted prevalence rates; all other analyses accounted for the complex sampling procedures of the NSDUH (e.g., oversampling youth and minorities) using the nesting (to capture stratification and to identify clustering) and weighting variables provided in the public use dataset. Maximum likelihood estimation was used to account for missing data in the indicator variables. Listwise deletion was utilized for missing data on predictor variables, and therefore individuals with missing

data on any of the covariate variables were excluded from all analyses. Individuals with missing data on distal outcomes were excluded from BCH analyses, but not from the LCA models.

Results

Participants and descriptive statistics. A total of 988 participants reported past-month tranquilizer or sedative misuse. Data from 18 participants were missing on predictor variables (1.8% of the total sample), and therefore 970 individuals were included in the LCA. All 18 participants with missing data did not answer the question regarding misuse behaviors (i.e., nonmedical use vs. medical misuse) and 10 of these participants were also missing data on motives for misuse. Participants with missing data on predictor variables were significantly more likely to endorse past-month hallucinogen use (27.8% vs. 12.3%; $X^2(1)=3.87$, $p=.049$), but did not differ from those with complete data on any other indicator variables. Those with missing data on predictor variables were also significantly more likely to identify as a racial/ethnic minority group (50% vs. 28.7%; $X^2(1)=3.91$, $p=.048$). An additional 39 participants were missing data on functional consequences (4.0% of the 970 participants included in the LCA) and were therefore excluded from distal outcome analyses. Participants with missing data on functional consequences were significantly more likely to report past-month marijuana use (71.8% vs. 55.7%; $X^2(1)= 3.92$, $p=.048$), past-month hallucinogen use (25.6% vs. 11.7%; $X^2(1)=6.75$, $p=.009$), be 18 to 25 years of age (74.4% vs. 46.5%; $X^2(1)=11.64$, $p=.001$), and identify as a racial/ethnic minority group (53.8% vs. 27.6%; $X^2(1)=12.61$, $p<.001$).

Sociodemographic, clinical, and substance use data for the 970 participants included in the LCA are reported in Table 1. Approximately half of the sample was female (52.9%), a majority (71.3%) identified as non-Hispanic white, and nearly half of the sample (47.6%) was between the ages of 18-25. A majority of the sample was employed full-time (47.5%) or reported an "other" employment status (e.g., keeping house, student; 24.3%) and completed a high school education (26.1%) or completed some college or an associate's degree (39.4%). The mean K6 score for the sample was 9.3 (SD=6.1; range=0-24; skewness=.41; kurtosis=-.52), indicating moderate levels of psychiatric distress (Prochaska, Sung, Max, Shi, & Ong, 2012).

Participants primarily reported past-month tranquilizer misuse only (82.5%), followed by sedative misuse only (11.5%) and the misuse of both tranquilizer and sedative medications in the previous month (6.0%). Approximately 74.9% of participants reported the use of tranquilizer/sedative medications without a prescription in the past 12 months. Participants reported a mean of 1.7 motives at their last episode of tranquilizer or sedative misuse (SD=1.1 SD=6.1; range=1-7; skewness=1.66; kurtosis=2.61).

The incidence and frequency of use for each substance category is presented in Table 2. Other than tranquilizers, binge alcohol use was the most frequently reported substance category, followed by marijuana and prescription opioid misuse. Notably, inhalant use was not included in the present analyses due to the low rate of use in the sample (*n*=26; 2.7% of the sample). Lastly, deviant behavior was the most commonly endorsed functional consequence in the present sample (27.6% of those with complete data), followed by suicidal ideation (21.6%), arrest (14.0%), intravenous drug use (8%), and diagnosis of a STI (7.8%).

Latent class analyses. BIC, aBIC, and entropy for the 1- through 4-class solutions for all three iterations of indicators are presented in Table 3. As previously described, models were first estimated for the LCA with binary (yes/no) indicators for past-month binge alcohol, marijuana, prescription opioid, cocaine, hallucinogen, heroin, and amphetamine use. In LCA iteration 2, binary indicators were retained for past-month marijuana, cocaine, hallucinogen, heroin, and amphetamine use, but indicators for the past-month frequency of use (0, 1–3, 4–8, 9–15, or 16–30 days) were utilized for binge alcohol use and prescription opioid misuse. Although marijuana use was also commonly reported, we chose to retain a binary indicator for marijuana use given that the majority of participants either did not use marijuana (43.7%) or misused marijuana at the highest possible frequency (16+ days of use; 31.8%). Finally, in LCA iteration 3, binary indicators were utilized for all substance categories included in the previous iterations (i.e., past-month binge alcohol, marijuana, prescription opioid, cocaine, hallucinogen, heroin, and amphetamine use), but two indicators were added to the models: a frequency indicator for past-month tranquilizer misuse and a binary indicator for past-month sedative misuse. A binary indicator was utilized for sedative misuse, as opposed to a frequency indicator, given the low rate of any sedative misuse in our sample (17.5%).

For all three LCA iterations, BIC and aBIC decreased from the 1- to 2-class models, from the 2- to 3-class models, and from the 3- to 4-class models. However, in all three iterations, the rate of decrease was greatest from the 1- to 2-class models. To prevent over-extraction of latent classes and to increase parsimony, we selected the 2-class solution of LCA iteration 3 as the final model. This solution was also chosen because of theoretical interpretability and classification precision (entropy=0.981). The

first latent class (tranquilizer misuse with high polysubstance use) comprised approximately 83.4% of the sample. This latent class was characterized by a 100% probability of reporting past-month tranquilizer misuse, high probabilities of binge alcohol use and marijuana use, and moderate probabilities of cocaine, prescription opioid, and amphetamine use. The second latent class (sedative misuse with low polysubstance use) consisted of approximately 16.6% of the sample and displayed a 100% probability of reporting past-month sedative misuse, moderate probabilities of binge alcohol, marijuana, and prescription opioid misuse, and low probabilities of all other substance use. The probabilities of endorsing each substance category, by latent class, are presented in Figure 1.

Given that the addition of past-month tranquilizer and sedative misuse improved classification precision, we examined the incidence of past-month substance use by tranquilizer misuse only, sedative misuse only, and both tranquilizer and sedative misuse (see Table 4). Consistent with findings from the LCA, those with past-month tranquilizer misuse (either alone or in combination with sedative misuse) had significantly higher rates of past-month use for all substances, with the exception of heroin and hallucinogens (likely due to inadequate power).

Logistic regression. Results of the logistic regression predicting expected membership in the LCA classes are presented in Table 5. The two older age groups were associated with lower odds of membership in the tranquilizer misuse with high polysubstance use class, as compared to the sedative misuse with low polysubstance use class (aOR=0.40, 95% CI=0.21, 0.76, p=0.005; aOR=0.27, 95% CI=0.14, 0.50, p<0.001; for 26-34 vs. 18-25 and 35+ vs. 18-25, respectively). In addition, a greater number of

motives for participants' last episode of misuse (aOR=1.87, 95% CI=1.19, 2.93, p=0.006) and nonmedical use in the past year (aOR=2.27, 95% CI=1.31, 3.91, p=0.003) were associated with greater odds of membership in the tranquilizer misuse with high polysubstance use class. Gender, racial/ethnic identity, and psychiatric distress were not significantly associated with class membership (ps>0.05)

Distal outcome analysis. Differences in functional outcomes by latent class are presented in Figure 2. Those in the tranquilizer misuse with high polysubstance use class had significantly higher rates of past-year arrest, as compared to the sedative misuse with low polysubstance use class (12.3% vs. 5.6%; $X^2(1)=4.17$, p =.041). However, there were no statistically significant differences between the two latent classes on any other functional outcome (p>0.05).

Discussion

The misuse of tranquilizer and sedative medications is an emerging public health problem that has been largely overlooked by clinicians, the scientific community, and policymakers (Lembke, Papac, & Humphreys, 2018). The present study aimed to address this gap in the literature by examining patterns of polysubstance use among a general population sample of adults with tranquilizer and sedative misuse. The present analysis identified two distinct latent classes of polysubstance use: tranquilizer misuse with high polysubstance use and sedative misuse with low polysubstance use. An expected majority of the sample (83.4%) demonstrated a pattern characterized by high probabilities of misusing tranquilizers and numerous other substances, such as binge drinking, marijuana, prescription opioids, cocaine, and amphetamines. These results indicate that a majority of tranquilizer misuse does not occur in isolation, but, rather, is part of a pattern of

polysubstance use. These findings corroborate consistent and robust associations between the use of other substances and risk of tranquilizer and sedative misuse (Votaw et al., in press).

The misuse of tranquilizer vs. sedative medications differentiated these two classes, given that model entropy increased substantially when these indicators were added to the model. Among NSDUH respondents, the most commonly misused tranquilizer products are benzodiazepines, while the most commonly misused sedatives are zolpidem products (though both categories include benzodiazepine products) (Hughes et al., 2016). Thus, polysubstance use might be particularly common among those with benzodiazepine misuse, but not among those who only misuse other tranquilizers and sedatives. Although numerous analyses of NSDUH data have combined tranquilizer and sedative categories (Becker et al., 2007; Goodwin & Hasin, 2002; Votaw et al., 2019), results of the present analysis indicate that those with tranquilizer vs. sedative misuse are distinct groups, with considerably different patterns of polysubstance use. These findings support a recent call by our research group to evaluate benzodiazepines separately from other tranquilizers and sedatives in population-based surveys (Votaw et al., in press). Pending this substantial change, researchers should consider tranquilizers and sedatives separate prescription drug classes when analyzing NSDUH data.

As hypothesized, younger age was associated with greater odds of membership in the tranquilizer misuse with high polysubstance use class. This is consistent with prior latent class analyses of epidemiological surveys finding that younger age is associated with high polysubstance use classes among those with alcohol use disorder (Moss, Goldstein, Chen, & Yi, 2015) and stimulant misuse (Chen et al., 2014). Educating young

adults about the harms of combining tranquilizers and sedatives with other substances might reduce rates of overdoses in this group.

Contrary to our hypothesis, and to other latent class analyses of polysubstance use among general population samples (Chen et al., 2014; Moss et al., 2015), gender was not associated with expected class membership. Other studies have also found few differences between women and men on tranquilizer and sedative misuse prevalence and consequences. Although men are generally at higher risk for alcohol and most illicit substance use, gender is not consistently associated with risk of tranquilizer and sedative misuse (Votaw et al., in press). Women and men who misuse tranquilizers and sedatives have similar rates of emergency department visits related to opioids and benzodiazepines (C. M. Jones & McAninch, 2015), injection benzodiazepine use (Shane Darke, Topp, & Ross, 2002; Ross, Darke, & Hall, 1997), treatment attrition (Schiff et al., 2007), and unsafe sex (Davies, Dominy, Peters, & Richardson, 1996). Thus, findings from the present analysis contribute to a growing body of literature indicating that women with tranquilizer and sedative misuse have similar profiles of substance use severity as men.

Psychiatric distress was also unrelated to latent class membership in the present analysis. Nevertheless, the sample as a whole reported elevated psychiatric distress, which is consistent with findings that psychiatric distress increases risk of tranquilizer and sedative misuse (Votaw et al., in press). It is important to note that we utilized a general measure of psychiatric distress. Previous studies have found that anxiety sensitivity is associated with benzodiazepine misuse frequency among those with opioid use disorder (McHugh et al., 2017), and that specific psychiatric disorders (e.g., major depressive disorder, social phobia, personality disorders) are associated with latent class

membership in high polysubstance use classes among those with alcohol use disorder (Moss et al., 2015). It is possible that specific measures of affective vulnerabilities and/or psychiatric disorders might be associated with polysubstance use among those with tranquilizer and sedative misuse. However, a latent class analysis examining patterns of polysubstance use among those with stimulant misuse found that the same measure of psychiatric distress used in the present analysis (K6 scores) was associated with membership in high polysubstance use classes (Chen et al., 2014). These findings indicate that psychiatric distress might not influence—or be influenced by—polysubstance use among those with tranquilizer or sedative misuse.

A greater number of motives for tranquilizer or sedative misuse was associated with membership in the tranquilizer misuse with high polysubstance use class. Those who use multiple substances might display more substance-specific motives for tranquilizer and sedative misuse, such as withdrawal relief and modifying the effects of other substances, in addition to more common motives, such as negative affect relief and enhancement. This is consistent with evidence that individuals with substance use disorders typically display multiple motives for benzodiazepine misuse (Votaw et al., in press). Accordingly, myriad factors might influence the development and maintenance of a pattern of polysubstance use among those with tranquilizer and sedative misuse. Cognitive-behavioral treatments for substance use disorders typically address craving, negative affect, decision-making, and interpersonal functioning (Carroll & Kiluk, 2017). Such multifaceted treatments might be particularly useful for reducing polysubstance use among those with tranquilizer and sedative misuse.

Those who reported nonmedical use of tranquilizer and sedatives (e.g., using without a prescription), as opposed to medical misuse (e.g., using at higher doses or for longer periods of time than prescribed), were also more likely to be classified in the tranquilizer misuse with high polysubstance use class. There are a number of potential explanations for this association. First, the most commonly misused drug in the tranquilizer category is alprazolam (Hughes et al., 2016), which is also one of the most commonly prescribed prescription medications in the U.S. (Lindsley, 2012). Therefore, tranquilizers might be more commonly diverted, and therefore available for use without a prescription, than medications in the sedative category. Those who display a pattern of polysubstance use might also have greater access to nonmedical sources of tranquilizers and sedatives, such as purchasing these medications from a drug dealer. Lastly, a third factor might influence both polysubstance use and likelihood of receiving tranquilizers/sedatives from nonmedical sources, such as impulsivity and perceptions of risk. As we previously noted in a systematic review, developing screening measures for benzodiazepine misuse should be a research priority (Votaw et al., in press). These screening measures might incorporate distinctions between nonmedical use and medical misuse in order to identify those who are at the greatest risk of polysubstance use and, by extension, overdose.

Interestingly, results of the distal outcomes analysis only identified one significant effect—those in the tranquilizer misuse with high polysubstance use class were significantly more likely to be arrested in the past year, as compared to those in the sedative misuse with low polysubstance use class. These findings might be explained by a greater likelihood of drug-related arrests among those with polysubstance use, such as

possession and trafficking. It is surprising that a high polysubstance use profile was not associated with other consequences of interest, including STI, injection drug use, deviant behaviors, and suicidal ideation. More broadly, these findings indicate that some associations between tranquilizer/sedative misuse and functional consequences *are not* attributable to polysubstance use. Yet, the examined functional consequences were highly prevalent among the whole sample of adults with past-month tranquilizer and sedative misuse (see Figure 2). These findings indicate that characteristics of those with tranquilizer and sedative misuse, such as elevated psychiatric distress, or pharmacological effects of tranquilizers and sedatives, such as disinhibition, might contribute to these functional consequences. However, information on overdose and several other consequences associated with misuse (e.g., treatment attrition, unsafe sex) was not available in the NSDUH survey, and therefore we cannot conclude that polysubstance use does not contribute to any consequences associated with tranquilizer and sedative misuse.

The present analysis is limited by several methodological features. First, data from the present study are cross-sectional and only include non-institutionalized, civilian citizens. Therefore, we cannot make temporal or causal conclusions about findings from the present analysis, and excluding certain subgroups (e.g., incarcerated individuals, those in substance use disorder treatment) might obscure population estimates of substance use. Although a relatively small proportion of our sample was missing data on predictor variables (1.8% of eligible respondents) or functional outcome variables (4.0% of those included in the LCA), those with missing data were significantly different than those without missing data on several LCA indicators. Unfortunately, M*Plus* cannot accommodate missing data techniques, such as multiple imputation, with complex survey

designs. The inability to include those with missing data on predictors or functional outcomes might influence the reliability and generalizability of study findings. In addition, information on several factors relevant to the research questions, including specific measures of psychiatric disorders (e.g., affective vulnerabilities, psychiatric diagnoses) and overdose, are not available in the NSDUH public use data file. Our findings also reflect the concurrent misuse of tranquilizers and sedatives with other substances, as opposed to simultaneous use (i.e., co-ingestion). Future studies are needed to examine patterns of simultaneous substance use among those with tranquilizer and sedative misuse.

In conclusion, a majority of individuals with tranquilizer or sedative misuse in a general population sample displayed a pattern of polysubstance use. The high polysubstance use class was also characterized by high probabilities of tranquilizer misuse and low probabilities of sedative misuse, likely indicating that polysubstance use is particularly common among those with benzodiazepine misuse. This finding is concerning, given that benzodiazepines increases risk of overdose when combined with other substances (J. D. Jones et al., 2012). It is important to note that the sedative with low polysubstance use class also had moderate probabilities of binge alcohol (approximately 36%), marijuana (17%), and prescription opioid misuse (18%), and therefore those with expected membership in this class might also be at heightened risk of overdose. Interventions to reduce polysubstance use and associated consequences among those with tranquilizer and sedative misuse should target young adults and those who report nonmedical use of these medications, and should address myriad motives for misuse. Longitudinal studies are needed to examine temporal relationships between

tranquilizer and sedative misuse onset, the development of a pattern of polysubstance use, and functional consequences.

Study 2: Clinical Sample

Method

Data source and participants. Participants were recruited from the inpatient detoxification unit of McLean Hospital (located in Belmont, Massachusetts) as part of a larger survey study characterizing individuals receiving inpatient detoxification treatment for substance use disorders. Inclusion criteria for this study required that participants were least 18 years of age, were receiving treatment for a substance use disorder, were not experiencing an acute medical/psychiatric disorder that would interfere with participation, and were not involuntarily admitted to treatment. The study was described to participants as research to understand how drugs and alcohol affect peoples' lives. If interested, participants first provided informed consent and then completed a battery of self-report questionnaire on an iPad, which took approximately 30 minutes to complete. Study staff could also read the survey to participants, if necessary (e.g., issues with eyesight, unfamiliar with iPads) or if requested by the participant. In addition, primary substance use disorder diagnoses were extracted from participants' medical charts.

Data collection for the larger study has been ongoing since 2013; four iterations (versions) of this study have been completed (N=1,351). Each version of the study includes distinct research questions, and therefore different questionnaires are included. For the present analysis, we combined all four versions and included respondents who reported past-month misuse of benzodiazepines or other tranquilizers/sedatives (N=451, 33.4% of those enrolled in the larger study). Participants were primarily receiving

treatment for opioid use disorder (*n*=263, 58.3% of the study sample) and alcohol use disorder (*n*=139, 30.8%), though a minority were receiving treatment for other substance use disorders (*n*=49, 10.9%).

Measures.

Sociodemographics. The following sociodemographic measures were included in the present analysis: sex and age. We chose not to include racial/ethnic identity as a predictor in this sample, given the low rate of respondents who did not identify as non-Hispanic White (6.4%).

Substance use. The Brief Addiction Monitor was utilized to assess past-month substance use (Cacciola et al., 2013). Participants reported their frequency of past-month use for the following substances: alcohol, benzodiazepines (benzos, Valium, Xanax, Ativan, Klonopin, clonazepam, etc.), other tranquilizers/sedatives (Ambien, barbs, Phenobarbital, downers, etc.), cocaine/crack cocaine, other stimulants (amphetamine, methamphetamine, Dexedrine, Ritalin, Adderall, speed, crystal meth, ice, etc.), heroin, other opioids (Oxycontin, oxycodone, Vicodin, Percocet, Morphine, Dilaudid, Demerol, codeine, Tylenol 3, Fentanyl, etc.), and inhalants (glue, adhesives, nail polish remover, paint thinner, etc.). Participants were instructed to only report illicit use or misuse of prescription substances and marijuana. Participants in Versions 1 and 2 reported frequencies of use, based on categorical response options (0, 1–3, 4–8, 9–15, or 16–30 days), while those in Versions 3 and 4 reported the total number of days they used the substance in the past-month, as a continuous response. All substance use responses were recoded into binary variables, indicating whether the participant used each substance in

the previous month (yes vs. no). Continuous frequencies of use in Versions 3 and 4 were recoded into the categorical frequencies used in Versions 1 and 2.

Physical and mental health. The Anxiety Sensitivity Index-3 (ASI-3) was included as a measure of anxiety sensitivity, or the fear of anxiety symptoms and sensations. Participants rate their agreement (e.g., "very little" to "very much") with a total of 18 items. Examples of items include the following: "I worry that other people will notice my anxiety.", "I think it would be horrible for me to faint in public.", and "It scares me when I blush in front of people." The potential range of responses ranged from 0 to 72, with higher scores representing greater anxiety sensitivity. Among participants in the present study with complete data on the ASI-3 (n=413), the measure demonstrated excellent internal consistency reliability (Cronbach's α=.93).

The Overall Anxiety Symptom and Impairment Scale (OASIS) was included as a measure of state anxiety that includes 5 questions about frequency, severity, and interference (e.g., avoidance, role impairment, social impairment) of anxiety symptoms in the previous week. Responses for each item range from 0 to 4, representing a potential range of scores from 0 to 20; higher scores indicate more anxiety symptoms and greater severity/interference of these symptoms (Campbell-Sills et al., 2009). Among participants in the present study with complete data on the OASIS (n=435), the OASIS demonstrated good internal consistency reliability (Cronbach's α=.87).

The Brief Pain Inventory (BPI) was used to measure chronic pain and pain interference with daily life. Participants were asked whether they had experienced any pain on the day they completed the survey, excluding pain from withdrawal. If participants responded affirmatively, they were asked to indicated the amount of time

they had been experiencing that pain. If participants reported experiencing pain for at least three months, they were categorized as having chronic pain. Those with chronic pain then answered 7 questions to determine the extent to which pain interferes with daily life, including interference with general activity, mood, walking activity, normal work, relationships, sleep and enjoyment of life. Response options ranged from 0 to 10, and total pain interference scores represented a mean of all 7 questions. Among those with chronic pain and complete BPI data in our sample (n=90), the pain interference subscale demonstrated excellent internal consistency reliability (Cronbach's α=.90). For the purpose of the present analysis, those without chronic pain were assigned a score of 0 on the pain interference variable. Two BPI variables were included in the present analysis: chronic pain and pain interference.

Proposed analyses. First, we utilized latent class analysis (LCA) to identify patterns of polysubstance use in the month prior to hospitalization. Indicators for the current analysis were past-month binge alcohol use and misuse of prescription medications (e.g., prescription amphetamines, prescription opioids) and illicit drugs (e.g., marijuana, cocaine, heroin, etc.). For substances that were endorsed by <5% of the sample, we either combined use of these substances with other substances of the same class (e.g., prescription opioids and heroin) or excluded these substances as an indicator in the LCA. We started with a 1-class solution and proceeded until the optimal model was identified. Model fit was assessed using the Bayesian Information Criteria (BIC), where a lower BIC indicates a better fitting model, and the sample size adjusted Bayesian Information Criteria (aBIC), which adds a penalty for increasing parameters related to sample size. The optimal number of classes was identified by the lowest BIC and aBIC

(or the greatest rate of decrease in BIC) and theoretical interpretability. Notably, we did not report the Lo-Mendell-Rubin adjusted likelihood ratio test (LRT) as an indicator of model fit given that M*Plus* does not provide LRT estimates when multiple imputation is utilized to account for missing data (see below for details on multiple imputation). We also evaluated classification precision using model entropy.

All models were estimated with three different combinations of indictors to identify the most theoretically interpretable model. First, indicators for the latent class analysis were included as binary (yes/no) past-month use of binge alcohol and illicit/prescription substances (LCA iteration 1). Second, for substances that were used by a high proportion of the sample in the previous month (i.e., >50%), categorical frequency indicators were utilized (LCA iteration 2). Lastly, a frequency indicator for past-month benzodiazepine misuse and a binary indicator for other tranquilizer/sedative misuse in the previous month were added to the model (LCA iteration 3).

Potential predictors of latent class membership were included as covariates in the LCA. Results are interpreted as a multinomial logistic regression, with latent class membership as a categorical outcome variable. Based on prior evidence of association with tranquilizer/sedative misuse incidence and severity (Votaw et al., in press), predictors for the clinical sample will include: age, gender, past-week anxiety symptoms (OASIS score), anxiety sensitivity (ASI-3 score), presence of chronic pain, and pain interference (BPI score). Effect sizes represent odds ratios, adjusting for all covariates in the model (aOR).

SPSS version 25 was used to prepare data; all other analyses were conducted in M*Plus* version 8 (L. Muthén & Muthén, 2017). Seventy-four participants (16.4% of the

total sample) were missing data on at least one predictor variable. As compared to those without missing data, participants with missing data on predictor variables were significantly older (*M* age=34.39 years vs. 30.89 years; $t(449)=-2.53$, $p=.012$), were more likely to report cocaine use in the previous month (63.5% vs. 50.5%; $X^2(1)=4.17$, $p=.041$), and were more likely to report 16+ days of use in the previous month for the following substances: benzodiazepines (40.5% vs. 26.5%; $X^2(1)=5.92$, $p=.015$), binge alcohol (35.6% vs. 23.3%; $X^2(1)=4.87$, $p=.027$), cocaine (27.0% vs. 8.0%; $X^2(1)=22.51$, $p<.001$), and prescription opioids (37.8% vs. 24.5%; $X^2(1)=5.59$, $p=.018$). Therefore, data were assumed to be missing at random (MAR), given that they were associated with other measured variables in the proposed models. Missing data were imputed using multiple imputation procedures in M*Plus* prior to calculating descriptive statistics and conducting the proposed latent class analyses (Asparouhov & Muthén, 2010). Parameter estimates were pooled across 50 imputed data sets. Imputation models included all indicators and covariates/predictors, as well as other variables of interest reported in descriptive statistics (e.g., employment, education, primary substance use disorder).

Results

Descriptive statistics. Sociodemographic, clinical, and substance use data are presented in Table 6. The sample was 31.5 years of age (*SD*=10.9), on average. A majority of the sample was male (69.3%), unemployed (58.6%), and received less than a college education (77.5%). Participants reported an average ASI-3 score of 28.1 (*SD*=16.5), representing high levels of anxiety sensitivity (Allan et al., 2014). This is consistent with evidence that high anxiety sensitivity increases risk of tranquilizer and sedative misuse (Conrod et al., 2000; Hearon et al., 2011; McHugh et al., 2017). The

sample reported a mean OASIS score of 12.8 (*SD*=4.3), which is comparable to scores reported by a sample of individuals with anxiety disorder diagnoses (Campbell-Sills et al., 2009). Given that the OASIS is a measure of anxiety symptoms in the past week, it is possible that high scores were influenced by acute withdrawal symptoms experienced during detoxification. A total of 31.1% of participants reported experiencing chronic pain, and the average level of pain interference among the whole sample (including those with and without chronic pain) was 1.5 (*SD*=2.6).

Participants primarily reported past-month benzodiazepine misuse only (73.7%), followed by the misuse of both benzodiazepines and other tranquilizers/sedatives (23.4%), and the misuse of other tranquilizers/sedatives only (2.9%). The incidence and frequency of use for each substance category is presented in Table 7. Other than benzodiazepines, binge alcohol use was the most frequently reported substance category, followed by prescription opioids, heroin, and marijuana. Inhalant use was not included in the present analyses due to the low rate of use in the sample (4.2% of the sample).

Latent class analyses. BIC, aBIC, and entropy for the 1- through 4-class solutions for all three iterations of indicators are presented in Table 8. As previously described, models were first estimated for the LCA with binary (yes/no) indicators for past-month binge alcohol, marijuana, prescription opioid, cocaine, heroin, stimulant, and other drug use. In LCA iteration 2, binary indicators were retained for past-month heroin, stimulant, and other drug use, but frequency indicators (0, 1–3, 4–8, 9–15, or 16–30 days) were utilized for substances used by >50% of the sample, including binge alcohol use, marijuana, prescription opioids, and cocaine. Although heroin use was reported by >50% of participants, the majority of participants either did not use heroin (39.4%) or misused

heroin at the highest possible frequency (16+ days of use; 46.8%). Finally, in LCA iteration 3, two indicators were added to the previous iteration: a frequency indicator for past-month benzodiazepine misuse and a binary indicator for other tranquilizer and sedative misuse.

For all three LCA iterations, BIC was lowest in the 2-class model, and highest in the 1-class model. aBIC decreased from the 1- to 2-class models, from the 2- to 3-class models, and from the 3- to 4-class models. However, in all three iterations, the rate of aBIC decrease was greatest from the 1- to 2-class models. To prevent over-extraction of latent classes and to increase parsimony, we selected the 2-class solution of LCA iteration 3 as the final model; this model was also chosen for theoretical interpretability. Entropy for this model indicated that approximately 76.4% of participants were likely classified correctly.

The probabilities of endorsing each substance category, by latent class, are presented in Table 9. The first latent class (opioid use with high polysubstance use) comprised approximately 73.1% of the sample. This latent class was characterized by high probabilities of heroin, binge alcohol, marijuana, prescription opioid, and cocaine use and moderate probabilities of stimulant and other drug use. The second latent class (binge alcohol use with moderate polysubstance use) consisted of approximately 26.9% of the sample and displayed high probabilities of binge alcohol use, moderate probabilities of marijuana, prescription opioid, and other drug use, and low probabilities of heroin, stimulant, and cocaine use. Interestingly, the binge alcohol use with moderate polysubstance use class had a higher probability of misusing benzodiazepines 16 or more days in the previous month (35.6% vs. 26.4%), while the opioid use with high

polysubstance use class had a higher probability of misusing non-benzodiazepine tranquilizers or sedatives in the previous month (29.7% vs. 16.9%).

Logistic regression. Results of the logistic regression predicting LCA class membership are presented in Table 10. Older age (aOR=0.89, 95% CI=0.85, 0.94, p<0.001) and higher anxiety sensitivity were (aOR=0.97, 95% CI=0.95, 0.99, p<0.030) associated with lower odds of membership in the opioid use with high polysubstance use class, as compared to the binge alcohol use with moderate polysubstance use class. Gender, anxiety symptoms, chronic pain status, and pain interference were not associated with class membership (*p*s>.05).

Discussion

The misuse of tranquilizer and sedative medications is associated with a range of poor outcomes among those with substance use disorders, most notably increased risk of overdose (Votaw et al., in press). Among those with substance use disorders, the use of other substances is consistently associated with increased risk of tranquilizer and sedative misuse (Votaw et al., in press). Yet, little is known about patterns of polysubstance use among those who misuse these medications. We identified two latent classes of polysubstance use among those in substance use disorder treatment who reported past-month tranquilizer/sedative misuse: opioid misuse with high polysubstance use and binge alcohol use with moderate polysubstance use. Notably, the opioid use with high polysubstance use class comprised over 70% of participants in our sample. It is concerning that a majority of participants with tranquilizer and sedative misuse displayed a high polysubstance use profile, given that tranquilizers and sedatives increase risk of overdose when combined with other substances (Gudin et al., 2013). Findings from the

present analysis also provide information on risk factors for a high polysubstance use profile that might help inform targeted prevention and treatment efforts.

Patterns of polysubstance use identified in the present analysis partially supported our hypothesis that we would identify three latent classes reflecting: (1) concurrent alcohol use, (2) concurrent opioid use, and (3) high levels of polysubstance use. Instead, two classes were identified and interpreted as opioid use with high polysubstance use and binge alcohol use with moderate polysubstance use. It is therefore possible that identified correlates of expected latent class membership might reflect factors associated with opioid use disorder vs. alcohol use disorder. Several item response probabilities identified in the present latent class analysis were somewhat surprising. In particular, the binge alcohol use with moderate polysubstance use class had a higher probability of misusing benzodiazepines 16 or more days in the previous month, as compared to the opioid use with high polysubstance use class (35.6% vs. 26.4%). This class also had a moderate probability of reporting past-month prescription opioid misuse, particularly at the highest frequency (16+ days; 28.4%). Given moderate to high probabilities of binge alcohol, benzodiazepine, and prescription opioid misuse, the binge alcohol use with moderate polysubstance use class might have similar overdose risk as the opioid use with high polysubstance use class.

As expected, younger age was associated with membership in the opioid use with high polysubstance use class. Findings on the association between age and risk of tranquilizer/sedative misuse have been inconsistent among those with substance use disorders (Votaw et al., in press). However, younger age is also associated with polysubstance use among individuals in substance use disorder treatment (Timko, Ilgen,

Haverfield, Shelley, & Breland, 2017) and those with opioid use disorder in the general population (Hassan & Le Foll, 2019). Psychoeducation on the risks of combining tranquilizers and sedatives with other substances should be targeted to young adults with substance use disorders.

Contrary to our hypothesis, gender was not associated with latent class membership. One previous study among those with opioid use disorder in the general population found that male gender was associated with greater polysubstance use (Hassan & Le Foll, 2019), but another study among those in substance use disorder treatment found that gender was not associated with polysubstance use patterns (Timko et al., 2017). Males comprised the majority of the sample in the present analysis (70%) and in the previous analysis of individuals in substance use disorder treatment (90%; Timko et al., 2017). Limited representation of female participants might have contributed to null findings. However, previous studies have not identified gender differences in risk of tranquilizer/sedative misuse (Votaw et al., in press) or in several consequences associated with misuse (e.g., hospitalizations, injection use, treatment attrition, HIV/HCV risk behaviors) (Davies et al., 1996; C. M. Jones & McAninch, 2015; Ross et al., 1997; Schiff et al., 2007). Although women might be more likely than men to misuse tranquilizers and sedatives to cope with negative affect (Votaw et al., in press), there appear to be few gender differences with respect to overall substance use severity. These findings underscore the need for research on sex and gender differences in the development and maintenance of benzodiazepine misuse.

Interestingly, anxiety sensitivity was associated with membership in the binge alcohol use with moderate polysubstance use class, as opposed to the opioid use with

high polysubstance use class. This unexpected finding might be explained by more frequent benzodiazepine misuse among those in the binge alcohol use with moderate polysubstance use class, given that anxiety sensitivity has previously been associated with higher frequency of benzodiazepine misuse among those with opioid use disorder (McHugh et al., 2017). Different motives for tranquilizer/sedative misuse between these two classes might also contribute to this finding. For example, those in the opioid use with high polysubstance use class could have more motives for tranquilizer and sedative misuse (e.g., to cope, for withdrawal, to get high, to modify the effects of other substances), while those in the binge alcohol use with moderate polysubstance use class might misuse these medications primarily to cope with negative affective and somatic states. Nevertheless, the magnitude of the association between anxiety sensitivity and latent class membership was small and the sample as a whole displayed a high level of anxiety sensitivity. Targeting anxiety sensitivity with psychosocial treatments (e.g., cognitive behavioral therapy) might help reduce tranquilizer/sedative misuse, regardless of polysubstance use profile.

Neither chronic pain nor pain interference was associated with latent class membership in the present analysis. However, two previous studies found that chronic pain and pain severity were associated with tranquilizer/sedative misuse among those with heroin use (Moses, Lundahl, & Greenwald, 2018) and injection drug use (Hassan & Le Foll, 2019). Accordingly, pain appears to be associated with tranquilizer and sedative misuse (either as an antecedent or consequence), but not necessarily with polysubstance use among those with misuse. This finding might also be explained by similar probabilities of prescription opioid misuse in both latent classes, given the strong link

between pain and risk of prescription opioid misuse (Voon, Karamouzian, & Kerr, 2017). Indeed, there is a robust and consistent association between the misuse of prescription opioids and tranquilizer/sedatives (Votaw et al., in press), and therefore previous findings indicating that pain is a risk factor for tranquilizer/sedative misuse might be confounded by prescription opioid misuse. Longitudinal studies are needed to elucidate these relationships. Specifically, it is unclear if individuals misuse tranquilizers and sedatives to relieve pain, if hyperalgesia is a consequence of misuse, or if the association between pain and tranquilizer/sedative misuse is attributable to prescription opioid misuse.

There are several limitations to the present analysis. First, neither causality nor temporality can be inferred from the present results given that this was a cross-sectional analysis. Second, individuals in the present analysis were receiving inpatient detoxification treatment, and therefore findings might not generalize to non-treatment-seeking individuals. In particular, scores on the OASIS and pain items might have been influenced by acute detoxification, even though participants were instructed to not report pain due to withdrawal. These findings might also have limited generalizability to racial and ethnically diverse populations, give than over 90% of the present sample identified as Non-Hispanic White. In addition, information was not collected on several factors that might help explain findings of the present analysis, such as motives for tranquilizer and sedative misuse and overdose history. Lastly, patterns of polysubstance use identified in the present analysis reflect the concurrent use of these substances, as opposed to co-ingestion. Given that co-ingestion contributes to drug overdose, future studies are needed to identify substances that are most commonly co-ingested with tranquilizers and sedatives.

In conclusion, a majority of those with tranquilizer and sedative misuse in the present analysis were classified in the opioid use with high polysubstance use class. Younger age was associated with membership in the opioid use with high polysubstance use class, indicating that psychoeducation on the risks of combining tranquilizers and sedatives with other substances could be particularly useful for young adults. Interventions targeting anxiety sensitivity might also have promise in reducing tranquilizer and sedative misuse, particularly among those with binge alcohol use and moderate polysubstance use. Addressing polysubstance use among those with tranquilizer/sedative misuse is critical to reduce overdose deaths involving these medications

Overall Conclusion

The overall aim of the present study was to examine patterns of polysubstance use among those with tranquilizer and sedative misuse in two distinct samples: those in the general population and those receiving substance use disorder treatment. A majority of individuals with tranquilizer and sedative misuse, both in the general population and among those in substance use disorder treatment, displayed high polysubstance use profiles. This is consistent with numerous previous analyses indicating that the use of multiple substances is a robust risk factor for tranquilizer and sedative misuse (Votaw et al., in press). These findings are concerning given that tranquilizers and sedatives increase risk of heart rate and respiratory depression when combined with other substances (Gudin et al., 2013).

We also aimed to examine correlates of latent class membership in order to identify potential risk factors for more severe polysubstance use. In the general

population sample, those in the tranquilizer misuse with high polysubstance use class were younger, displayed more motives for misuse, and were more likely to misuse tranquilizers/sedatives without a prescription. In the clinical sample, the opioid use with high polysubstance use class was also younger and had lower anxiety sensitivity. However, as a whole, the general population sample reported elevated levels of psychiatric distress and the clinical sample had anxiety sensitivity scores similar to those reported by individuals with anxiety disorders. Taken together, young adults with tranquilizer and sedative misuse and those who report misuse without a prescription might benefit from targeted interventions to reduce polysubstance use, including psychoeducation. Prevention and treatment efforts should address negative affect, including anxiety sensitivity, as well as the range of motives for which tranquilizers and sedatives are used, including coping with negative affective and somatic states, getting high, and modifying other drug effects.

Lastly, we examined functional consequences associated with identified latent classes. The primary reason for this aim was to determine if functional consequences previously associated with tranquilizer/sedative misuse (e.g., STI, suicidal ideation, criminality, injection drug use) might be partly attributable to polysubstance use. However, those in the tranquilizer misuse with high polysubstance use class only differed from those in the sedative misuse with low polysubstance use class on one consequence—rates of past year arrest. Instead, both latent classes displayed high rates of examined functional consequences, including STI, injection drug use, deviant behaviors, and suicidal ideation. These findings indicate that characteristics of those with tranquilizer or sedative misuse, such as elevated psychiatric distress, or pharmacological

effects of tranquilizers and sedatives, such as disinhibition, might contribute to these functional consequences.

These two analyses have several shared methodological limitations. Data from both studies are cross-sectional and were based on retrospective, self-report measures. Therefore, we are not able to draw temporal or causal inferences from study findings, and findings might be influenced by recall bias. Both studies also utilized LCA, which is probabilistic and has been criticized for reifying subgroups that do not exist (Raudenbush, 2005). Accordingly, latent classes identified in the present analysis should be interpreted as a heuristic for heterogeneity in polysubstance use among those with tranquilizer and sedative misuse. Misclassification of participants in expected latent classes could also cause spurious associations between predictors and expected latent class membership, and between expected latent class membership and functional outcomes (see Kamata, Kara, Patarapichayatham, & Lan, 2018). Lastly, we evaluated a limited number of predictors of latent class membership in both studies, primarily due to constraints on measures that were administered. It is possible that we overlooked relevant variables, such as specific measures of psychiatric distress in the general population sample and motives for tranquilizer/sedative misuse in the clinical sample.

Future research in this area is needed to determine if the use of other substances precedes or follows the initiation of tranquilizer and sedative misuse, as well as motives for these transitions. Such studies could help inform optimal timing and content for prevention and treatment efforts to reduce polysubstance use among those with tranquilizer and sedative misuse. As previously reviewed, there is also an urgent need for screening measures to detect tranquilizer/sedative misuse (Votaw et al., in press). It

would be valuable to determine the extent to which predictors of high polysubstance use classes in the present analyses (e.g., younger age, nonmedical use) are useful for detecting individuals at the highest risk of consequences related to tranquilizer and sedative misuse. Lastly, longitudinal studies could help identify mechanisms underlying the associations between tranquilizer/sedative misuse and poor functional outcomes, such as behavioral disinhibition and increased psychiatric distress. Continued research in this area has the potential to improve outcomes among those with tranquilizer and sedative misuse, including reducing rates of overdose.

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Tables

Table 1. Sociodemographic, clinical, and substance use characteristics of the general population sample (*N*=970)

Variable	*N*	Mean (SD) or Percent
Gender		
Male	457	47.1%
Female	513	52.9%
Age		
18-25	462	47.6%
26-34	227	23.4%
>35	281	28.9%
Race/Ethnicity		
Non-Hispanic White	692	71.3%
Black/African American	92	9.5%
Hispanic	114	11.8%
Multiple Racial/Ethnic Identities	52	5.4%
Other Racial/Ethnic Identity	20	2.1%
Educational Attainment		
Less than high school	146	15.1%
High school graduate	253	26.1%
Some college/associates degree	382	39.4%
College graduate	189	19.5%
Family Income		
<$20,000	283	29.2%
$20,000-$49,999	310	32.0%
$50,000-$74,999	132	13.6%
>$75,000	245	25.3%
Psychiatric Characteristics		
K6 Score	970	9.3 (6.1)
Substance Use Characteristics		
Past-month tranquilizer misuse only	800	82.5%
Past-month sedative misuse only	112	11.5%
Past-month tranquilizer and sedative misuse	58	6.0%
Nonmedical use	727	74.9%
Number of motives for misuse	970	1.7 (1.1)

Table 2. Incidence and frequency of past-month substance use among the general population sample (*N*=970)

	No Use		Any Use		1-3 Days of Use		4-8 Days of Use		9-15 Days of Use		16+ Days of Use	
	n	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%
Tranquilizers	115	11.6%	873	88.4%	534	54.0%	193	19.5%	87	8.8%	59	6.0%
Sedatives	815	82.5%	173	17.5%	105	10.6%	34	3.4%	23	2.3%	11	1.1%
Binge Alcohol Use	376	38.8%	594	61.2%	251	25.9%	186	19.2%	98	10.1%	59	6.1%
Marijuana	423	43.6%	547	56.4%	81	8.4%	83	8.6%	75	7.7%	308	31.8%
Prescription Opioids	626	64.5%	344	35.5%	133	13.7%	81	8.4%	62	6.4%	68	7.0%
Cocaine	825	85.1%	145	14.9%	91	9.4%	31	3.2%	12	1.2%	11	1.2%
Hallucinogens	851	87.7%	119	12.3%	95	9.8%	16	2.6%	4	0.4%	4	0.4%
Heroin	910	93.8%	60	6.2%	15	1.5%	10	1.0%	6	0.6%	29	3.0%
Amphetamines	746	76.9%	224	23.1%	--	--	--	--	--	--	--	--

Note: Given the low rate of methamphetamine use in our sample (5.4%), methamphetamine use was combined with prescription amphetamine use. Therefore, frequency of use for the overall amphetamine class is unavailable.

Table 3. Indicators of model fit for the 1- through 4-class solutions for all three iterations of indicators in the general population sample

Iteration 1: Indicators of Model Fit for Latent Class Analysis with Binary Indicators

	1-Class Solution	2-Class Solution	3-Class Solution	4-Class Solution
Bayesian Information Criteria (BIC)	22178.288	6070.813	6001.443	5993.644
Adjusted BIC	22111.591	6000.941	5883.931	5828.492
Entropy	1.000	0.656	0.721	0.699

Iteration 2: Indicators of Model Fit for Latent Class Analysis with Frequency Indicators for Binge Alcohol Use and Prescription Opioid Use

	1-Class Solution	2-Class Solution	3-Class Solution	4-Class Solution
Bayesian Information Criteria (BIC)	24488.868	8365.167	8297.486	8330.245
Adjusted BIC	24403.115	8257.183	8122.806	8088.869
Entropy	1.000	0.660	0.723	0.705

Iteration 3: Indicators of Model Fit for Latent Class Analysis with Frequency Indicator for Tranquilizer Misuse and Binary Indicator for Sedative Misuse

	1-Class Solution	2-Class Solution	3-Class Solution	4-Class Solution
Bayesian Information Criteria (BIC)	25861.012	9450.388	9151.231	9032.268
Adjusted BIC	25778.435	9348.756	8986.079	8803.596
Entropy	1.000	0.981	0.785	0.811

Table 4. Incidence of past-month substance use by sedative misuse only, tranquilizer misuse only, and sedative and tranquilizer misuse for the total general population sample (*N*=988)

	Past-Month Sedative Misuse Only (*n*=115)	Past-Month Tranquilizer Misuse Only (*n*=815)	Past-Month Sedative and Tranquilizer Misuse (*n*=58)	
Substance Category	*n* (%)	*n* (%)	*n* (%)	X^2
Binge Alcohol Use	56 (48.7%)	514 (63.1%)	37 (63.8%)	8.93*
Marijuana Use	31 (27.0%)	489 (60.0%)	36 (62.1%)	45.56**
Cocaine Use	8 (7.0%)	128 (15.7%)	12 (20.7%)	7.63*
Prescription Opioid Misuse	28 (24.3%)	288 (35.3%)	35 (60.3%)	21.88**
Heroin Use	4 (3.5%)	51 (6.3%)	6 (10.3%)	3.19
Hallucinogen Use	8 (7.0%)	109 (13.4%)	7 (12.1%)	3.80
Amphetamine Use	14 (12.2%)	189 (23.2%)	25 (43.1%)	20.81**

Note: *p<0.05, **p<0.001

Table 5. Logistic regression examining predictors of membership in the tranquilizer with high polysubstance use class in the general population sample

Variable	*b* (SE)	aOR (95% CI)	*p*
Gender			
Male	Ref	Ref	
Female	-0.50 (0.29)	0.61 (0.35, 1.07)	0.085
Age			
18-25	Ref	Ref	
26-34	-0.92 (0.33)	0.40 (0.21, 0.76)	0.005
35+	-1.32 (0.32)	0.27 (0.14, 0.50)	<0.001
Race			
Non-Hispanic White	Ref	Ref	
Racial/Ethnic Minority	0.057 (0.40)	1.06 (0.48, 2.34)	0.887
Number of motives for misuse	0.63 (0.23)	1.87 (1.19, 2.93)	0.006
Nonmedical use			
No	Ref	Ref	
Yes	0.82 (0.28)	2.27 (1.31, 3.91)	0.003
Psychiatric distress (K6 Score)	0.03 (0.03)	1.03 (0.98, 1.09)	0.240

Table 6. Sociodemographic, clinical, and substance use characteristics of the clinical sample (*N*=451)

Variable	Mean (SD) or Percent
Sex	
Male	69.3%
Female	30.7%
Age	31.5 (10.9)
College Graduate	
No	77.5%
Yes	22.5%
Employed	
No	58.6%
Yes	41.4%
Psychiatric Characteristics	
ASI-3 score	28.1 (16.5)
OASIS score	12.8 (4.3)
Physical Health Characteristics	
Presence of chronic pain (% yes)	31.1%
Pain interference score	1.5 (2.6)
Substance Use Characteristics	
Past-month benzodiazepine misuse only	73.7%
Past-month other tranquilizer/sedative misuse only	2.9%
Past-month benzodiazepine and other tranquilizer/sedative misuse	23.4%

Table 7. Incidence and frequency of past-month substance use among the clinical sample (*N*=451)

	No Use	Any Use	1-3 Days of Use	4-8 Days of Use	9-15 Days of Use	16+ Days of Use
	%	%	%	%	%	%
Benzodiazepines	2.9%	97.1%	27.9%	22.6%	17.7%	28.8%
Other Tranquilizers/ Sedatives	73.7%	26.3%	12.0%	5.8%	2.9%	5.5%
Binge Alcohol Use	36.4%	63.6%	14.5%	11.4%	12.4%	25.3%
Marijuana	39.4%	60.6%	15.4%	8.7%	9.6%	26.9%
Prescription Opioids	37.6%	62.4%	13.8%	13.6%	8.2%	26.8%
Cocaine	47.4%	52.6%	17.4%	12.7%	11.3%	11.2%
Heroin	39.4%	60.6%	4.2%	5.6%	4.0%	46.8%
Stimulants	66.9%	33.1%	14.1%	8.3%	5.4%	5.4%
Other Drugs	69.5%	30.5%	7.6%	10.2%	6.5%	6.2%

Table 8. Indicators of model fit for the 1- through 4-class solutions for all three iterations of indicators in the clinical sample

Iteration 1: Indicators of Model Fit for Latent Class Analysis with Binary Indicators

	1-Class Solution	2-Class Solution	3-Class Solution	4-Class Solution
Bayesian Information Criteria (BIC)	17390.800	4074.617	4084.034	4119.751
Adjusted BIC	17330.501	4007.971	3972.957	3964.244
Entropy	1.000	0.775	0.680	0.675

Iteration 2: Indicators of Model Fit for Latent Class Analysis with Frequency Indicators for Binge Alcohol, Prescription Opioid, Heroin, and Cocaine Use

	1-Class Solution	2-Class Solution	3-Class Solution	4-Class Solution
Bayesian Information Criteria (BIC)	20305.087	7016.821	7064.091	7140.872
Adjusted BIC	20206.704	6874.008	6838.763	6833.03
Entropy	1.000	0.767	0.754	0.781

Iteration 3: Indicators of Model Fit for Latent Class Analysis with Frequency Indicator for Benzodiazepine Misuse and Binary Indicator for Other Tranquilizer/Sedative Misuse

	1-Class Solution	2-Class Solution	3-Class Solution	4-Class Solution
Bayesian Information Criteria (BIC)	22171.924	8905.147	8947.178	9044.745
Adjusted BIC	22057.673	8730.597	8674.246	8673.43
Entropy	1.000	0.764	0.736	0.756

Table 9. Probabilities of endorsing each substance category by latent class in the clinical sample

	Opioid Use with High Polysubstance Use	Binge Alcohol Use with Moderate Polysubstance Use
Benzodiazepines		
No Use	3.3%	1.7%
1-3 Days	26.4%	32.1%
4-8 Days	25.4%	15.2%
9-15 Days	18.5%	15.4%
16+ Days	26.4%	35.6%
Other Tranquilizers & Sedatives (% Yes)	29.7%	16.9%
Binge Alcohol		
No Use	41.2%	23.5%
1-3 Days	17.0%	7.7%
4-8 Days	13.6%	3.2%
9-15 Days	11.7%	14.5%
16+ Days	16.5%	49.1%
Marijuana		
No Use	29.9%	65.3%
1-3 Days	16.6%	4.2%
4-8 Days	10.4%	4.2%
9-15 Days	11.4%	4.4%
16+ Days	31.7%	14.0%
Cocaine		
No Use	34.0%	83.9%
1-3 Days	21.4%	6.4%
4-8 Days	16.8%	1.6%
9-15 Days	14.5%	2.7%
16+ Days	13.3%	5.4%
Prescription Opioids		
No Use	38.6%	56.6%
1-3 Days	15.7%	8.6%
4-8 Days	17.2%	3.8%
9-15 Days	10.3%	2.6%
16+ Days	26.2%	28.4%
Stimulants (% Yes)	40.0%	14.3%
Heroin (% Yes)	80.2%	7.3%
Other Drugs (% Yes)	32.6%	24.7%

Table 10. Logistic regression examining predictors of membership in the opioid misuse with high polysubstance use class

Variable	*b* (SE)	aOR (95% CI)	*p*
Gender			
Female	Ref	Ref	
Male	0.43 (0.43)	1.53 (0.66, 3.54)	0.317
Age	-0.12 (0.03)	0.89 (0.85, 0.94)	<0.001
Anxiety Sensitivity (ASI-3 Score)	-0.03 (0.01)	0.97 (0.95, 0.99)	0.030
Anxiety Symptoms (OASIS Score)	0.05 (0.05)	1.05 (0.95, 1.16)	0.357
Presence of Chronic Pain			
No	Ref	Ref	
Yes	1.01 (0.91)	2.75 (0.47, 16.28)	0.264
Pain Interference (BPI score)	-0.06 (0.15)	0.95 (0.70, 1.28)	0.721

Figures

Figure 1. Probabilities of endorsing each substance by latent class in the general population sample

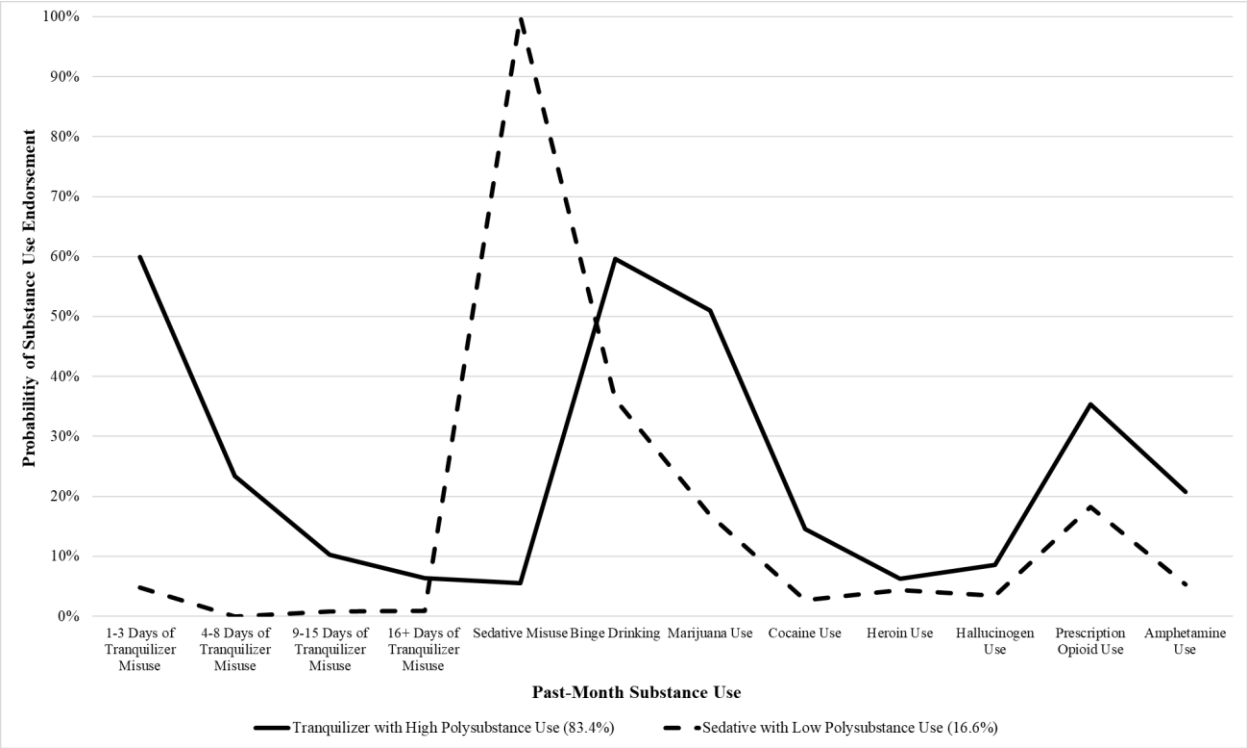
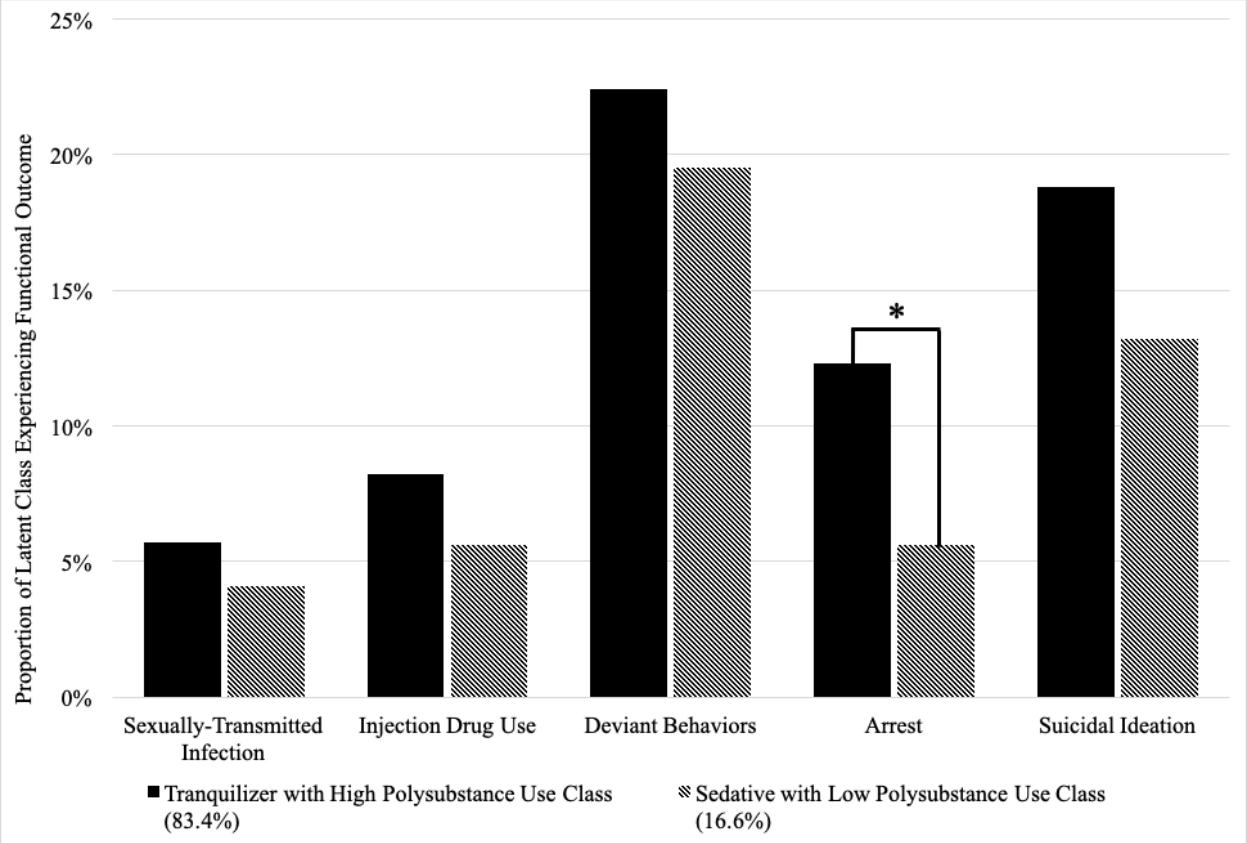


Figure 2. Differences in functional outcomes by latent class in the general population sample



Note: *$p<0.05$