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TRANQUILIZER/SEDATIVE MISUSE AND PATTERNS OF POLYSUBSTANCE USE

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Patterns of Polysubstance Use Among Adults with Tranquilizer or Sedative Misuse

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Abstract

The misuse of tranquilizer and sedative medications (e.g., benzodiazepines) is associated with myriad negative sequelae. In particular, the misuse of these medications increases risk of overdose when combined with other substances, such as opioids or alcohol. Yet, little is known about other substance use among those who misuse tranquilizers and/or sedatives. This study characterized subgroups of individuals with tranquilizer or sedative misuse, based on patterns of other substance use. Data were extracted from the 2015-2016 National Survey on Drug Use and Health; adult respondents with past-month tranquilizer or sedative misuse were included ($N=970$). Latent class analysis identified two classes: (1) tranquilizer misuse with high polysubstance use (approximately 83.3% of the sample), and (2) sedative misuse with low polysubstance use (16.7%). Correlates of expected membership in the tranquilizer misuse with high polysubstance use class included younger age, more motives for misuse, use without a prescription, and higher chance of past-year arrest. The two latent classes did not significantly differ on rates of suicidal ideation, deviant behaviors, sexually transmitted infection, and injection drug use. These results indicate that a majority of tranquilizer misuse does not occur in isolation, but, rather, is part of a pattern of polysubstance use. This finding is concerning given that tranquilizer misuse increases risk of overdose when combined with other substances.

Keywords: sedatives, tranquilizers, benzodiazepines, polysubstance use, National Survey on Drug Use and Health

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Introduction

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 2017, approximately 2.2% of U.S. citizens ages 12 and older misused tranquilizers (e.g., clonazepam, alprazolam, buspirone, cyclobenzaprine), making them the third most commonly misused illicit or prescription substance (Center for Behavioral Health Statistics and Quality, 2018). An additional 0.5% misused sedative medications (e.g., zolpidem, barbiturates, temazepam, triazolam) (Center for Behavioral Health Statistics and Quality, 2018). The high prevalence of tranquilizer and sedative misuse is concerning because misuse is associated with myriad negative sequelae. Most notably, overdose deaths involving benzodiazepines (often in combination with other substances) increased more than 300% from 2002-2015 (National Institute on Drug Abuse, 2017). It is not yet known, however, whether misuse of tranquilizers and sedatives occurs outside of the context of other substance use or whether these substances are predominantly misused as part of a pattern of polysubstance use (Votaw, Geyer, Rieselbach, & McHugh, 2019). We aimed to address this gap in the literature by characterizing adults with tranquilizer or sedative misuse in the general population, based on patterns of other substance use.

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

In the general population, polysubstance use and other substance use disorders increase risk of tranquilizer and sedative misuse (Blanco, Han, Jones, Johnson, & Compton, 2018; Maust, Lin, & Blow, 2019; Schepis, Teter, Simoni-Wastila, & McCabe, 2018). Accordingly, rates of tranquilizer and sedative misuse are elevated among those with substance use disorders. Among those with opioid use disorder, approximately 50% of treatment-seekers (McHugh et al., 2017;

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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 19% among treatment-seekers (McHugh, Geyer, Karakula, Griffin, & Weiss, 2018) and 2.7% in the general population (Votaw, Witkiewitz, et al., 2019). 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 (McHugh et al., 2018; Schuman-Olivier et al., 2013; Votaw, Witkiewitz et al., 2019).

The high prevalence of tranquilizer and sedative misuse among those with substance use disorders might be partly explained by the many functions that these medications can serve in this population. Tranquilizers and sedatives are most commonly misused to reduce negative affective (e.g., anxiety) and somatic (e.g., insomnia) states (Center for Behavioral Health Statistics and Quality, 2018). However, individuals with opioid misuse 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 (Mateu-Gelabert et al., 2017; Stein et al., 2016). 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 multiple reasons, thus increasing the overall prevalence of misuse.

Correlates of Tranquilizer and Sedative Misuse

Several studies have identified factors that are uniquely associated with tranquilizer and sedative misuse, even when controlling for other substance use. Among those in the general

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population and those with substance use disorders, psychiatric disorders, greater general psychiatric distress, and affective vulnerabilities (e.g., anxiety sensitivity) increases risk of tranquilizer/sedative misuse (Blanco et al., 2018; McHugh et al., 2018, 2017; Schepis et al., 2018). Sociodemographic factors consistently associated with misuse include young adulthood (Blanco et al., 2018; Maust et al., 2019) and non-Hispanic white identity (Becker, Fiellin, & Desai, 2007; Votaw, Witkiewitz, et al., 2019). Although several large, population-based studies indicate that female gender is associated with tranquilizer and sedative misuse (Becker et al., 2007; Ford, Reckdenwald, & Marquardt, 2014), males typically have higher risk of misuse when controlling for receipt of a tranquilizer or sedative prescription (Fenton, Keyes, Martins, & Hasin, 2010; Maust et al., 2019). Indeed, receipt of a tranquilizer or sedative prescription is also associated with greater odds of tranquilizer or sedative misuse (Fenton et al., 2010).

Functional Consequences Associated with Tranquilizer and Sedative Misuse

The most consistent consequence of tranquilizer and sedative misuse is increased risk of opioid overdose (Mateu-Gelabert et al., 2017; Moses, Lundahl, & Greenwald, 2018; Stein, Anderson, Kenney, & Bailey, 2017). In addition, tranquilizer and sedative misuse is associated with infectious disease (Bach et al., 2016; Ickowicz et al., 2015), risky sexual behavior/risky injection practices (Ickowicz et al., 2015; Tucker et al., 2016), increased criminal involvement (Comiskey, Stapleton, & Kelly, 2012; Darke et al., 2010; Horyniak et al., 2016), suicidal ideation/attempt (Artenie, Bruneau, Roy, et al., 2015; Artenie, Bruneau, Zang, et al., 2015; Han, Compton, Blanco, & Jones, 2018; Schepis et al., 2018), and poor substance use disorder treatment outcomes (Darke et al., 2010; Naji et al., 2016).

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

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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; Wines et al., 2004), whereas others have suggested that those with tranquilizer or sedative misuse might have greater psychological 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 consequences (Votaw, Geyer et al., 2019), but this hypothesis has not been systematically investigated.

Current Study

Most studies characterizing tranquilizer and sedative misuse have enrolled samples with severe substance use presentations, particularly those with opioid use disorder (Votaw, Geyer et al., 2019). Although there is robust evidence to suggest that those with polysubstance use are the most vulnerable to tranquilizer and sedative misuse (Votaw, Geyer 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 in a general population sample. We hypothesized that a high polysubstance use class would be the most prevalent in our sample. The second aim of the study was to examine sociodemographic, clinical, and substance use correlates of identified latent classes. We hypothesized that male gender, younger age, white race, greater psychological distress, more motives for misuse, and use without a prescription would be associated with greater probability of expected membership in the high polysubstance use class. Lastly, we examined functional consequences associated with identified latent classes, and hypothesized

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that individuals with expected classification in the high polysubstance use class would display the highest proportions of functional consequences, such as criminality, suicidal ideation, and sexually transmitted infection.

Method

Data source and Participants

This study extracted data from the National Survey on Drug Use and Health (NSDUH), which is an annual, population-based survey of U.S. citizens ages 12 and older. 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 in the present analysis were adult respondents who reported the misuse of tranquilizer or sedative medications in the previous month and had complete data on all predictor variables ($N=970$). 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 (Schepis et al., 2018; Votaw, Witkiewitz et al., 2019).

Measures

Sociodemographics. The following sociodemographic measures were included in the present analysis: gender (which in NSDUH is subjectively assigned by the interviewer or by participants' self-identified gender identity, if their gender identity is unclear to the interviewer),

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age (categorized as 18-25 years old, 26-34, 35-49, 50+), 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, temazepam, 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/frequency 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 and the frequency of past-year and past-month misuse.

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. For the present analysis, continuous past-month substance use frequencies 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).

Tranquilizer and sedative 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?”

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Response options included the following: used without my own prescription, used in greater amounts than prescribed, used more often than prescribed, used over longer periods of time than prescribed, and used in some other way that was not directed by a physician. Participants were able to choose more than one misuse behavior. Responses were recoded into a dichotomous variable representing any misuse of tranquilizer or sedative medications without a prescription in the past year (termed nonmedical use) or only misusing one's own prescription for longer periods of time, at higher doses, or for longer periods of time than prescribed (termed medical misuse).

To determine motives for tranquilizer and sedative misuse, participants were asked about the reasons for their most recent use: "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?" 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 with feelings/emotions, to increase/decrease the effect(s) of another drug, because I'm hooked/have to have tranquilizers/sedatives, and some other reason. Participants could choose more than one reason, 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.

Psychological distress. The measure of psychological distress utilized in the present analysis 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

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adult respondents. This scale is a general measure of psychological distress that includes six questions about the frequency of mood and anxiety symptoms, such as nervousness, hopelessness, and restlessness. The scale has a potential range of scores from 0 to 24, with higher scores indicating greater psychological distress in the previous month.

Functional consequences. Consistent with previous analyses using NSDUH data (Chen et al., 2014; Hedden et al., 2010), past-year deviant behavior was determined by self-reported endorsement of attacking someone with the intent to seriously hurt them, selling illegal drugs, or attempting to steal anything worth more than \$50. Past-year arrest status was determined by a question that asked participants how many times they have been arrested and booked in the previous year, not including minor traffic violations. Participants self-reported suicidal ideation by indicating if they seriously thought about trying to kill themselves in the previous year. 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 episode of injection drug use. Finally, sexually transmitted infection was determined by self-reported diagnosis of chlamydia, gonorrhea, herpes, or syphilis by a clinician.

Statistical Analyses

Latent class analysis (LCA) was utilized to identify patterns of polysubstance use in the previous month. Indicators for the current analysis were past-month (yes/no) misuse of prescription medications (e.g., prescription opioids), illicit drugs (e.g., marijuana, cocaine, heroin, etc.), and binge alcohol use. Given the low rates of methamphetamine (4.6%) and inhalant use (2.0%) in the present sample, methamphetamine use was combined with prescription amphetamine misuse and inhalant use was not included in the analysis. We also included a frequency indicator for past-month tranquilizer misuse (0, 1–3, 4–8, 9–15, or 16–30

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days) and a binary (yes/no) indicator for past-month sedative misuse. We tested two additional combinations of indicators (e.g., frequencies of past-month substance use, exclusion of tranquilizer and sedative misuse), but the current combination resulted in the most precise and theoretically interpretable model. Results from LCA models with other combinations of indicators are available in Supplementary Materials.

The LCA was first estimated with a 1-class solution and increasing number of classes were estimated until the optimal model was identified. The optimal number of classes was identified by the greatest rate of decrease in or lowest Bayesian Information Criteria (BIC) and sample size adjusted Bayesian Information Criteria (aBIC) and theoretical interpretability. The Lo-Mendell-Rubin adjusted likelihood ratio test (LRT) was not reported or interpreted as an indicator of model fit because LRT estimates do not account for complex sampling designs, such as those used by the NSDUH (Muthén, 2016). Model entropy, a measurement of classification precision, was also interpreted and reported, with entropy greater than .80 indicating good classification precision.

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, Geyer et al., 2019), and included: gender, age (18-25, 26-34, 35-49, 50+), 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. Results are interpreted as a logistic regression and effect sizes reported are adjusted odds ratios (aOR), controlling for all covariates in the model.

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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 weighs 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 past-year functional consequences that have previously been associated with tranquilizer and sedative misuse (Votaw, Geyer et al., 2019), including the following: deviant behavior, arrest, suicidal ideation, injection drug use, and sexually transmitted infection.

SPSS version 25 was used to prepare data; all other analyses were conducted in *MPlus* version 8 (Muthén & Muthén, 2017). We utilized the nesting and weighting variables provided in the public use dataset to account for the complex sampling procedures of the NSDUH (e.g., stratification and clustering, oversampling youth and minorities) using. 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. 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

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missing data on motives for misuse. 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.

Results

Descriptive Statistics

Individuals with sedative or tranquilizer misuse in the previous month with complete data on covariates were included as participants in analyses ($N=970$). Overall, 84.5% of participants misused tranquilizers in the previous month, with 50.7% of the sample reporting 1-3 days of misuse, 19.5% reporting 4-8 days of misuse, 8.7% reporting 8-15 days of misuse, and 5.5% reporting 16 or more days of misuse. Sedative misuse was reported by 21.2% of the sample, and 5.7% of the sample reported misusing both tranquilizers and sedatives. Other than tranquilizers and sedatives, participants most commonly reported binge alcohol use (55.8%), followed by marijuana (45.4%), prescription opioids (32.6%), amphetamines (including both prescription amphetamines and methamphetamine; 18.1%), cocaine (12.6%), hallucinogens (7.7%), and heroin (6.0%).

Latent Class Analysis

BIC, aBIC, and entropy for the 1- through 4-class latent class analysis solutions are presented in Table 1. 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, the rate of decrease was greatest from the 1- to 2-class models. Further evaluation of the 2-class model indicated excellent classification precision (entropy=0.981) and theoretical interpretability. Therefore, we selected the 2-class solution as the final model to prevent over-extraction of latent classes and to increase parsimony.

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The first latent class, which we labeled “tranquilizer misuse with high polysubstance use,” comprised approximately 83.3% 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, which we labeled “sedative misuse with low polysubstance use,” consisted of approximately 16.7% 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.

Logistic Regression

Results of the logistic regression predicting expected membership in the latent classes, with the sedative misuse with low polysubstance use as the reference class, are presented in Table 2. The three 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=0.32, 95% CI=0.15, 0.68, $p=0.003$; aOR=0.22, 95% CI=0.10, 0.47, $p<0.001$; for 26-34 vs. 18-25 and 35-49 vs. 18-25, and 50+ vs. 18-25, respectively). In addition, a greater number of motives for participants’ last episode of misuse (aOR=1.83, 95% CI=1.21, 2.76, $p=0.004$) and nonmedical use in the past year (aOR=2.12, 95% CI=1.31, 3.65, $p=0.003$) were associated with greater odds of membership in the tranquilizer misuse with high polysubstance use class. Gender, racial/ethnic identity, and psychological distress were not significantly associated with class membership ($ps>0.05$)

Distal Outcome Analysis

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Differences in functional consequences by expected latent class membership are presented in Figure 2. Those with expected membership 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 ($p>0.05$). Importantly, the current sample of individuals with past month sedative or tranquilizer misuse reported much higher rates of past-year functional consequences, as compared to those in 2015-2016 NSDUH adult respondent sample without past-month tranquilizer or sedative misuse ($N=85,198$), including for deviant behavior (21.9% vs. 2.3%), arrest (11.3% vs. 2.0%), suicidal ideation (17.8% vs. 3.9%), injection drug use (7.8% vs. 0.3%), and sexually transmitted infection (5.4% vs. 2.0%).

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 past-month tranquilizer or 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 (83.3%) demonstrated a pattern characterized by high probabilities of misusing tranquilizers and numerous other substances, such as binge drinking, marijuana, prescription opioids, cocaine, and amphetamines. Even those in the sedative with low polysubstance use class had moderate probabilities of binge alcohol, marijuana, and prescription opioid misuse. These results indicate

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that a majority of tranquilizer and sedative 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, Geyer et al., 2019).

The misuse of tranquilizer vs. sedative medications appeared to differentiate these two classes. Among NSDUH respondents, the most commonly misused tranquilizer products are benzodiazepines, whereas 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. Although numerous analyses of NSDUH data have combined the tranquilizer and sedative categories (Schepis et al., 2018; Votaw, Witkiewitz 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. Furthermore, those with expected classification in the sedative with low polysubstance use class had very low probabilities of tranquilizer misuse (see Figure 1). These findings support a recent call by our research group to evaluate benzodiazepines separately from other tranquilizers and sedatives in population-based surveys (Votaw, Geyer et al., 2019). 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,

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2015) and stimulant misuse (Chen et al., 2014). Educating young adults about the harms of combining tranquilizers with other substances might reduce rates of overdoses in this group.

Contrary to our hypothesis, gender was not associated with expected class membership. Other latent class analyses of polysubstance use patterns among general population samples have found that high polysubstance use is more common among males (Chen et al., 2014; Moss et al., 2015), however, our results did not find an association between gender and likelihood of membership in one class relative to the other. 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, Geyer et al., 2019). Women and men who misuse tranquilizers and sedatives have similar rates of emergency department visits related to opioids and benzodiazepines (Jones & McAninch, 2015), injection benzodiazepine use (Darke, Topp, & Ross, 2002; Ross, Darke, & Hall, 1997), treatment attrition (Schiff, Levit, & Moreno, 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.

Psychological distress was also unrelated to latent class membership in the present analysis. Nevertheless, the sample as a whole reported moderate psychological distress ($Mean=8.5$; Prochaska, Sung, Max, Shi, & Ong, 2012), which is consistent with findings that psychological distress increases risk of tranquilizer and sedative misuse (Votaw, Geyer, et al., 2019). A latent class analysis examining patterns of polysubstance use among those with stimulant misuse found that the same measure of psychological distress used in the present analysis (K6 scores) was associated with membership in high polysubstance use classes (Chen et

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al., 2014). These findings indicate that psychological distress might not be associated with polysubstance use among those with tranquilizer or sedative misuse.

It is important to note that we utilized a general measure of psychological 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.

A greater number of motives for tranquilizer or sedative misuse was associated with expected 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, Geyer et al., 2019). Accordingly, many 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 promising for the treatment of polysubstance use among those with tranquilizer and sedative misuse.

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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, Geyer et al., 2019). 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. It is surprising that a high polysubstance use profile was not associated with other consequences of interest, including sexually transmitted infection, injection drug use, deviant behaviors, and suicidal ideation. These findings might

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indicate that associations between tranquilizer/sedative misuse and some functional consequences are not entirely 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. These findings indicate that characteristics of those with tranquilizer and sedative misuse, such as elevated psychological 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 previously 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 had several methodological limitations. First, data from the present study are cross-sectional, only include non-institutionalized, civilian citizens, and were from retrospective, self-report measures. 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. Findings might also be influenced by recall bias. In addition, this study 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 consequences (see Kamata, Kara, Patarapichayatham, & Lan, 2018).

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In conclusion, a majority of individuals with tranquilizer or sedative misuse in a general population sample displayed a pattern of high polysubstance use. This 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 (Jones, Mogali, & Comer, 2012). It is important to note that the sedative with low polysubstance use class 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 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.

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Table 1. Indicators of model fit for the 1- through 4-class solutions

	BIC	aBIC	Entropy
1-class	26667.742	26578.813	1.000
2-class	9454.893	9350.085	0.981
3-class	9160.868	8989.364	0.786
4-class	9048.253	8810.054	0.812

Note: BIC = Bayesian Information Criteria, a measure of model fit, in which the optimal number of classes is indicated by the lowest BIC; aBIC = Adjusted Bayesian Information Criteria, adds a penalty to the BIC estimate for increasing parameters related to sample size. 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 (Muthen, 2016). However, all analyses were conducted without the inclusion of complex sampling variables. These analyses supported the 2-class solution as the final model. Specifically, using the LRT we found a 2-class model fit significantly better than the 1-class model, the 3-class model *did not* fit significantly better than the 2-class model, and the 4-class model *did not* fit significantly better than the 3-class model.

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Table 2. Logistic regression examining predictors of expected membership in the tranquilizer with high polysubstance use class with the sedative misuse with low polysubstance use as the reference class.

Variable	<i>b</i> (SE)	aOR (95% CI)	<i>p</i> -value
Gender			
Male	Ref	Ref	
Female	-0.50 (0.28)	0.61 (0.35, 1.06)	0.078
Age			
18-25	Ref	Ref	
26-34	-0.92 (0.33)	0.40 (0.21, 0.76)	0.005
35-40	-1.15 (0.39)	0.32 (0.15, 0.68)	0.003
50+	-1.52 (0.39)	0.22 (0.10, 0.47)	<0.001
Race			
Non-Hispanic White	Ref	Ref	
Racial/Ethnic Minority	0.07 (0.41)	1.07 (0.48, 2.41)	0.869
Number of motives for misuse	0.60 (0.21)	1.83 (1.21, 2.76)	0.004
Nonmedical use			
No	Ref	Ref	
Yes	0.78 (0.26)	2.12 (1.31, 3.65)	0.003
Psychological distress (K6 Score)	0.03 (0.03)	1.03 (0.98, 1.08)	0.283

Note. *b* (SE) = unstandardized regression coefficient (standard error); aOR (95% CI) = adjusted odds ratio with 95% confidence interval. Ref = Reference class for each nominal covariate.

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Figure 1. Probabilities of endorsing each past-month substance category by latent class

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Figure 2. Differences in past-year functional consequences by latent class

Note: * $p < 0.05$

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