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High enhancer, downer, withdrawal helper: Multifunctional nonmedical benzodiazepine use among young adult opioid users in New York City

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Abstract

Background—Benzodiazepines are a widely prescribed psychoactive drug; in the U.S., both medical and nonmedical use of benzodiazepines has increased markedly in the past 15 years. Long-term use can lead to tolerance and dependence, and abrupt withdrawal can cause seizures or other life-threatening symptoms. Benzodiazepines are often used nonmedically in conjunction with other drugs, and with opioids in particular a combination that can increase the risk for fatal and non-fatal overdose. This mixed-methods study examines nonmedical use of benzodiazepines among young adults in New York City and its relationship with opioid use.

Methods—For qualitative analysis, 46 90-minute semi-structured interviews were conducted with young adult opioid users (ages 18–32). Interviews were transcribed and coded for key themes. For quantitative analysis, 464 young adult opioid users (ages 18–29) were recruited using Respondent-Driven Sampling and completed structured interviews. Benzodiazepine use was assessed via a self-report questionnaire that included measures related to nonmedical benzodiazepine and opioid use.

Conflict of Interest

All authors have no conflicts of interests to declare.

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Results—Participants reported using benzodiazepines nonmedically for a wide variety of reasons, including: to increase the high of other drugs; to lessen withdrawal symptoms; and to come down from other drugs. Benzodiazepines were described as readily available and cheap. There was a high prevalence (93%) of nonmedical benzodiazepine use among nonmedical opioid users, with 57% reporting regular nonmedical use. In bivariate analyses, drug-related risk behaviours such as polysubstance use, drug bingeing, heroin injection and overdose were strongly associated with regular nonmedical benzodiazepine use. In multivariate analysis, growing up in a middle-income household (earning between \$51,000 and \$100,000 annually), lifetime overdose experience, having ever used cocaine regularly, having ever been prescribed benzodiazepines, recent drug bingeing, and encouraging fellow drug users to use benzodiazepines to cope with opioid withdrawal were consistently strong predictors of regular nonmedical benzodiazepine use.

Conclusion—Nonmedical benzodiazepine use may be common among nonmedical opioid users due to its drug-related multi-functionality. Harm reduction messages should account for the multiple functions benzodiazepines serve in a drug-using context, and encourage drug users to tailor their endorsement of benzodiazepines to peers to include safer alternatives.

Keywords

nonmedical prescription opioid use; young adults; nonmedical benzodiazepine use; heroin use; drug use

Introduction

Benzodiazepines, which include alprazolam (e.g. Xanax), clonazepam (e.g. Klonopin), diazepam (e.g. Valium), and lorazepam (e.g. Ativan), among others, are a class of psychoactive drug that are widely prescribed in the U.S., most commonly for anxiolytic and muscle-relaxant purposes (National Institute on Drug Abuse, 2014). Approved for treating various conditions including panic attacks, anxiety, seizures and alcohol withdrawal, they enhance the effect of the neurotransmitter gamma-aminobutyric acid (GABA), resulting in sedative, hypnotic, anxiolytic, anticonvulsant and muscle relaxant properties (Longo & Johnson, 2000; White & Irvine, 1999). While safe and effective for short-term use, long-term benzodiazepine use can be problematic due to the development of tolerance and dependence (Ashton, 2005). Physiologic dependence on benzodiazepines can cause seizures and other life-threatening symptoms if withdrawal is abrupt and managed improperly (Ashton, 2005; Puntillo, Casella, & Reid, 1997).

Between 1996 and 2013, the percentage of adults filling a benzodiazepine prescription increased from 4.1% to 5.6% (Bachhuber et. al, 2016). Paralleling this increase, nonmedical benzodiazepine use has become a growing problem in the U.S. According to the Substance Abuse and Mental Health Services Administration (SAMHSA) Treatment Episode Data Set (TEDS), drug treatment admissions for nonmedical benzodiazepine use tripled between 1998 and 2008, while overall treatment admissions increased by only 11 percent (TEDS Report, 2011). Benzodiazepines are often used nonmedically in conjunction with other drugs; while only 12.9% of persons admitted to treatment between 1998 and 2008 reported benzodiazepines as their primary drug, 82.1% reported them as secondary (SAMHSA, 2011). Between 2005 and 2011, there were nearly one million emergency department visits

involving benzodiazepines, used either alone or in combination with other drugs, most commonly opioids and/or alcohol (SAMHSA, 2014). Overdose-related deaths involving benzodiazepines also increased from 0.58 per 100,000 adults in 1999 to 3.07 in 2013 (Bachhuber, et. al, 2016).

Despite emergency room and treatment admission data signalling a significant and growing public health problem, research on nonmedical benzodiazepine use is limited. Recent work includes McCabe's (2005) analysis of national survey data from a random sample of American college students, 7.8% of whom reported past-year nonmedical benzodiazepine use. Similarly, in a recent study of high school seniors, McCabe and West (2014) found that 7.5% of youth reported lifetime nonmedical benzodiazepine use. Among those (4.9%) who reported ever having a prescription for benzodiazepines, more than half (59.4%) reported lifetime nonmedical use. Nonmedical benzodiazepine use is especially common among individuals using other drugs (McCabe, 2005; SAMHSA, 2012). A 2011 study of young adult "club drug" users who also misuse prescription drugs found benzodiazepines were the most commonly misused prescription drug, with 86.8% of participants reporting nonmedical benzodiazepine use in the past 90 days and 25.0% meeting DSM-IV criteria for benzodiazepine abuse and/or dependence (Kurtz, Surratt, Levi-Minzi, & Mooss, 2011). Dwyer's (2005) ethnographic study concluded that the main motivation for benzodiazepine injection among Vietnamese heroin users was the pursuit of intense pleasure.

Concurrent with rising rates of nonmedical benzodiazepine use, the U.S. is in the midst of an opioid use epidemic, with rates of heroin use more than doubling over the past decade (Centers for Disease Control and Prevention, 2015). These heroin users are often young people who embarked upon long-term opioid use and dependence via nonmedical prescription opioid use (Jones, Logan, Gladden, & Bohm, 2015; Mateu-Gelabert, Guarino, Jessell, & Teper, 2015). The relationship between nonmedical opioid and benzodiazepine use has been previously established (Chen et al., 2011; Gelkopf, Bleich, Hayward, Bodner, & Adelson, 1999; Khosla, Juon, Kirk, Astemborski & Mehta, 2011; Ross, Darke, & Hall, 1996). Studies have found benzodiazepines are often procured from doctors and illicit sales to mitigate withdrawal symptoms from other drugs, including opioids, and, conversely, to intensify or prolong their effects (Jones, Mogali, & Comer, 2012; Lankenau et al., 2012; Liebrezn et al., 2015; O'Brien, 2005). Havens, Walker and Leukefeld's (2010) study of Appalachian prescription opioid users found that approximately half of participants (48%) had used benzodiazepines nonmedically in the past 30 days. Participants described lengthy histories of benzodiazepine use, reporting a mean of eight years of use, with a quarter reporting over 13 years of use. National treatment admissions data from the U.S. reveal that, as rates of opioid use have increased, so too have rates of the co-use of opioids and benzodiazepines; admissions for the nonmedical co-use of prescription opioids and benzodiazepines have increased by 569.7 percent from 2000 to 2010 (SAMHSA, 2012). Similarly, other researchers have documented frequent use of benzodiazepines among people who inject drugs (Bramness & Komer, 2007; Darke, Ross, Teesson, & Lynskey, 2003; Darke et. al., 2010; Dwyer, 2008; Evans, Halm, Lum, Stein, & Page, 2009; Forsyth, Farquhar, Gemmell, Shewan, & Davies, 1993; Fry & Bruno, 2002; Lavellen Hammersley, & Forsyth, 1991; Smith, Tett, & Hall, 2010; Strang, Griffiths, Abbey, & Gossop, 1994).

The nonmedical use of benzodiazepines among opioid users is a serious concern as benzodiazepines can markedly increase the harmful effects of opioids, particularly risk for fatal and non-fatal overdose (Chan, Stajic, Marker, Hoffman, & Nelson, 2006; Dietze, Jolley, Fry, & Bammer, 2005; Dilokthornsakul et al., 2016; Jann, Kennedy, & Lopez, 2014; Jones & McAninch, 2015; Kerr et al., 2007; Perret, Deglon, Kreek, Ho, & La Harpe, 2000; Toblin, Paulozzi, Logan, Hall, & Kaplan, 2010; White & Irvine, 1999). While opioids are the most common drug class involved in overdose, most overdoses involve more than one substance (McGregor, Darke, & Christie, 1998; Oliver & Keen, 2003; Ward & Barry, 2001; Wunsch, Nakamoto, Behonick, & Massello, 2009). In New York City, the location where the present study takes place, the NYC Department of Health and Mental Hygiene recently found that 79% of overdose deaths involved an opioid. However, 97% of overdose deaths involved more than one substance; benzodiazepines were a frequent substance involved in overdose deaths, found in 55% of methadone, 53% of prescription opioid, and 41% of heroin-related overdose deaths (Paone, Tuazon, Nolan, & Mantha, 2015).

Given the broad and significant role benzodiazepines play as both primary and secondary drugs of misuse, and their association with overdose risk, more work is needed to explore patterns of nonmedical benzodiazepine use, especially among opioid users. The present analysis contributes to this research by reporting findings related to nonmedical benzodiazepine use among young adult nonmedical prescription opioid and/or heroin users in New York City.

Methods

This mixed-methods paper, part of a study designed to assess risks associated with opioid use, examines patterns, contexts, motivations for and correlates of benzodiazepine use among New York City young adults who use prescription opioids nonmedically and/or use heroin. Qualitative data explore the contexts, motivations for and consequences of participants' nonmedical benzodiazepine use and are presented to assist in the interpretation of quantitative results. Quantitative data report key variables related to young adults' nonmedical benzodiazepine use, including frequency of use, age of initiation and experiences of overdose.

Qualitative Data Collection and Analysis

Qualitative data are presented to provide context in understanding how and why benzodiazepine use takes place among young adult opioid users. The qualitative portion of the analysis includes data from 46 participants who were interviewed in the formative phase of the study. Eligibility for qualitative interviews was determined through self-report using a brief verbal screening protocol. Participants were deemed eligible by meeting the following criteria: live in one of the five boroughs of New York City; report lifetime use of prescription opioids for nonmedical reasons (most reported use in the past 30 days); speak English or Spanish, and be able to provide informed consent.

Interviews were semi-structured, and lasted approximately 90 minutes each. Participants received a small monetary compensation at the conclusion of the interview. Topical domains addressed in interviews included drug-use trajectories, social contexts of opioid use, and

sexual and drug-using networks and practises. All participants were asked about their initiation into drug use, including their age at initiation of each major class or form of drug use (e.g., prescription opioids, benzodiazepines, heroin) and route of administration (e.g., oral, intranasal, injection), as well as the context in which it occurred. Questions were open-ended, allowing participants to introduce and elaborate upon issues relevant to their opioid use, and included probes about experiences related to their use of prescription drugs in general, including benzodiazepines. When reporting experiences of drug use and/or overdose, participants described episodes that included the use of opioids as well as other drugs. Opioid use often occurred in combination with the use of other substances such as alcohol and other prescription drugs (e.g., benzodiazepines) and/or illicit drugs (e.g., marijuana). In qualitative interviews, participants often used “Xanax” as a common street name to refer to any benzodiazepine. We have no way to determine when “Xanax” was used to refer to the specific drug alprazolam or when it was used as a generic reference to any of the multiple benzodiazepines available.

Interviews were digitally audio-recorded and transcribed verbatim. ATLAS.ti, a software program, was used to facilitate the coding and analysis of qualitative data. Interviews were read to identify all quotes related to benzodiazepine use and then analysed using semantic thematic analysis (Braun & Clark, 2006; Patton, 2002). Following this semantic approach, the explicit meaning of participants’ words served as the basis for thematic coding. Themes were identified on the basis of recurring patterns of meaning dominant throughout multiple participants’ accounts. Most themes reflected a utilitarian use of benzodiazepines as an instrument to facilitate or manage participants’ ongoing opioid use (e.g. enhancing high, managing withdrawal, etc.), or the overdose risk associated with combining benzodiazepines with opioids. These discrete themes were then unified under the overarching category of “multifunctional benzodiazepine use”. All names have been changed to pseudonyms to protect participants’ confidentiality. Some transcriptions have been slightly edited for clarity and readability. Further details on the 46 participants included in the qualitative sample are provided elsewhere (Frank et al., 2015; Jessell et al., 2015, Mateu-Gelabert et al., 2015).

Quantitative Data Collection and Analysis

The 464 participants in the quantitative portion of the study were recruited using Respondent- Driven Sampling (RDS), a form of chain-referral sampling designed to engage hard-to-reach populations. In this method, participants are recruited by means of their personal network connections (Heckathorn, 1997, 2002; McKnight et al., 2006). The process began with the selection by research staff of 20 eligible young adult opioid users to serve as RDS “seeds”. These seeds were recruited directly from the community, from among qualitative interviewees, as well as through referrals from service providers and other research studies. After being screened for eligibility, participants were interviewed and invited to refer up to three eligible peers from their opioid-using contacts to participate in the study. This process was repeated with the seeds’ recruits and for successive sample waves.

Eligibility criteria included: nonmedical use of prescription opioids and/or heroin use in the past 30 days; current residence in New York City; 18–29 years old; English-speaking; and ability to provide informed consent. To determine eligibility, interviewers used a verbal and

visual screening protocol that included: self-report of past-30-day opioid use; a point-of-care urine screen for methadone, opiates and oxycodone; a quiz in which participants were asked to identify pictures of prescription opioids; and, for those who reported recent drug injection, a visual assessment for injection marks. Participants who appeared to be age 25 or older were asked to verify their age with photo identification. Participants were paid US\$60.00 for completing the interview and an additional incentive for each eligible participant they referred. At the initiation of recruitment, US\$20 was paid for each referral; later, in order to increase the number of referrals per participant, incentives were increased to: US\$40, \$50 and \$60 for first, second and third referral, respectively.

Structured, computer-assisted interviews lasted between 90–120 minutes and included questions on drug use history and current use, overdose, drug treatment and mental health. The questionnaire also inquired about participants' nonmedical use of prescription drugs, defined as the "use of prescription drugs not prescribed for the respondent or use of these drugs only for the experience or feeling they caused." (SAMHSA, 2011)

In structured assessments and statistical analyses, "regular" use of any drug was defined as using that drug three or more times a week for at least one month. "Overdose" was defined as any time a participant "lost consciousness, stopped breathing or was unresponsive as a result of drug use." "Binging" on drugs (assessed for the past 30 days) was defined as any time a participant "used considerably more of a drug than usual or mixed more drugs than usual in one sitting."

All statistical analyses were conducted in the program R versions 3.2.2 and 3.2.4 (R Core team, 2015), with specific R packages used as noted. Multiple imputation was conducted using the R package MICE (Van Buuren & Groothuis-Oudshoorn, 2011) to impute missing network size data for a portion of the sample. RDS population estimates (presented in Tables 1 and 2) were then calculated using the successive sample estimator (Gile, 2011) in the R package RDS (Handcock, Fellows, & Gile, 2012), using a working population size of 15,000. Results were not sensitive to working population size.

Characteristics of participants were summarised with and without stratification by lifetime regular (i.e., 3 or more times per week) benzodiazepine use. Relationships between regular benzodiazepine use and those characteristics selected as independent variables were also examined, using both standard statistical methods and specialized methods for RDS data.

Bivariate analyses were first conducted using standard inferential statistical techniques. Log ratios and p-values were computed between all binary variables using a Wald chi-square test, and the 95% confidence interval was calculated.

In order to account for the dependence within an RDS sample, bivariate analyses were then re-run using a novel permutation test developed by study collaborators (Kim, Gile, Guarino, & Mateu-Gelabert, 2016). In an RDS sample, respondents are recruited by other respondents; thus standard tests for association are subject to bias due to the non-random nature of the sample selection. Based on their relative positions in the RDS sampling structure, pairs of respondents are more or less likely to be similar. The permutation test method uses a dependent permutation distribution to form a null distribution of the test

statistic in a population with a sampling and dependence structure like the one observed, but with no association between the variables, an approach which allows for valid tests of association when using data derived from RDS samples. Table 3 presents standard odds ratios and p-values alongside the p-values from permutation tests.

Regression-style modeling and multivariate analysis are not technically valid for RDS data because of the complex dependence in the samples. However, because multivariate analysis to study the impacts of some covariates while controlling for others is a standard practice, and because point estimates for coefficients should not be as strongly impacted by the RDS dependence as the standard errors, we have conducted a set of multivariate analyses as a descriptive addition to highlight findings that seem particularly strong or robust.

Multivariate analysis (glm, stats package, R version 3.2.4) was conducted on all variables that had a p-value of $< .05$ based on the bivariate odds ratio result. Multivariate analysis was conducted in several steps so as to best understand the relationships, both temporal and categorical, among the variables. First, based on the nature of the variables and their probable temporal relation to the period in which participants engaged in regular benzodiazepine use, we grouped the variables into four categories: 1) sociodemographics (prior to regular nonmedical benzodiazepine use): race, ethnicity and household income growing up; 2) lifetime drug use variables (of closer temporal proximity to benzodiazepine use but could have occurred before, during or after such use): overdose, regular heroin use, regular nonmedical prescription stimulant use, regular cocaine use, regular heroin injection; 3) lifetime mental health variables (also of uncertain temporal status in relation to regular nonmedical benzodiazepine use): experienced serious anxiety, received treatment for anxiety, prescribed benzodiazepines, and participation in drug treatment; and 4) post-benzodiazepine use variables (variables that represent recent behaviours that are likely to have occurred after the participant started engaging in regular nonmedical benzodiazepine use): used benzodiazepines at last overdose, binged on drugs in the past 30 days, and encouraged others to use benzodiazepines to cope with opioid withdrawal.

To determine the strongest and most robust set of correlates, controlling for other variables, we connected a series of logistic regressions. We first examined each of the four subsets of variables, and then studied the drug use and mental health correlates conditional on the strongest demographic predictors. We next considered the strongest demographic, drug use and mental health correlates together, and finally, considered the post-benzodiazepine group of correlates along with the strongest correlates from the other three groups. For simplicity, we present only the model fit including the strongest predictors in each of the categories. Adjusted p-values are based on adjusted odds ratios. In our discussion of findings, we discuss correlates with consistently strong odds ratios and strong nominal significance levels across models.

Results

Qualitative Findings

Of the 46 qualitative interviewees, 27 were male, 18 female, and one was transgender-female. Participants were a mean of 25.3 years old ($SD = 3.9$ years; range = 18–32 years).

Thirty-two identified as White/Caucasian, 3 as African American/Black, 9 as Hispanic/Latino, and 2 as Asian/Pacific Islander. Fourteen attended some high school, 9 had received a high school diploma or GED, and 23 had attended or graduated college.

In response to interview questions regarding participants' use of opioids, the use of benzodiazepines arose frequently and parallel to participants' opioid use. The following themes emerged from the data and are described in more detail below: concomitant initiation into benzodiazepine and prescription opioid use; polysubstance use including concurrent nonmedical use of benzodiazepines with opioids; varied motivations for benzodiazepine use; and overdose experiences related to benzodiazepine use.

Many participants described first using prescription opioids nonmedically during their teenage years in social settings with peers (e.g. gatherings with friends) and in combination with other pills and/or drugs, including benzodiazepines. Benzodiazepines, like prescription opioids, were often first provided by friends, as we have reported elsewhere (Mateu-Gelabert et al., 2015). Elizabeth (19, White, Female), for example, described first using alcohol, marijuana, benzodiazepines and prescription opioids all around the same time. *"So my first time with drugs I was fourteen... [I used] weed, alcohol, and then pills, so like Xanax ... I started smoking weed, I started drinking... and then I started taking Xanax and codeine... with friends.."*

As their drug use developed over time, participants described a process in which they moved from casual use in social settings to more regular polysubstance use. Many participants described regularly using opioids in combination with benzodiazepines. For example, Robin (24, White, Female), described using heroin and prescription opioids in conjunction with benzodiazepines. *"Probably every time, every time I do an opiate, I usually take a benzo... cause it increases the high. So it's very easy to get prescribed too, like I'm prescribed."* Similarly, Nestor (24, Male, Latino) described his daily use as involving both Xanax (a benzodiazepine) and Percocet (a prescription opioid). *"[I use Percs at night] In the morning, I'd probably take like two Xanax, boom, the most. Every day probably two Xanax."* Other participants described using benzodiazepines only when they were easily accessible, or to help them through opioid withdrawal, or to "come down" from other drugs, while others did not use them at all or avoided using them because of negative experiences with the drug in the past.

Participants who did use benzodiazepines, however, reported doing so for a variety of drug-related purposes, and because they are easily accessible benzodiazepines are often easy to obtain and relatively inexpensive. Participants such as Robin described diverted benzodiazepines as widely available in illicit markets. *"I usually end up buying Xanax... Xanax is big business in New York, so a lot of people sell them."* Other participants, like Chrystal (30, Female, White), said that they were able to get benzodiazepines prescribed from various doctors. *"I get prescribed all kinds of things... I have three doctors that give me Xanax."* In addition, participants like Elizabeth remarked on how cheap benzodiazepines were, especially in comparison to prescription opioids, and how, at times, they were even given them for free. *"Usually I get it [Xanax] for free. Sometimes I pay for it one of my friends is prescribed it... mainly it's free."*

Participants reported a variety of motivations for using benzodiazepines nonmedically, often in conjunction with other drugs. Benzodiazepines were described as enhancing the high of opioids, supplementing the opioid high when participants did not have enough opioids, helping participants to “come down” from other drugs, such as crack or cocaine, and/or helping participants self-manage mental health problems such as anxiety. Some participants used benzodiazepines to help them withdraw from opioids and cope with withdrawal symptoms. David (29, Male, White), for example, described using buprenorphine and naloxone (Suboxone) in combination with Xanax to help him “kick” his opioid dependence.

“Suboxone doesn't really take the anxiety and the edge off like Xanax does. When you mix it with Suboxone, it makes the withdrawal a lot easier, and I've noticed this just recently. I've kicked, tried to kick three times in the past three months, and Suboxone by itself hasn't really helped on some of them... Yeah [Xanax takes] the edge off the anxiety. I mean, that's why they call it kicking, because you kick your foot with anxiety, you know, and there's the anxiousness from not having the drug in your system.”

Similarly, after Rick (26, Male, White) and his friends witnessed another friend overdosing, he increased his use of benzodiazepines in an attempt to “wean” himself off opioids.

“Me and at least a couple other kids were like, yeah, we should chill out on this [opioid use]. But then it was like, oh, I'm addicted to it, like. And so I struggled with that for a while trying to wean off of it. But then I started taking the Xanax more cause that helps, you know, it helped me get off the painkillers.”

Other participants (e.g. Jeremy 27, Male, White), described using benzodiazepines to enhance the high from opioids, including methadone, Suboxone, other prescription opioids and heroin.

Heroin like really makes you feel like really, really good when you first get into it. And then after a while, like you're really using it to feel normal you're not like getting that high. [...] But if you've eaten Xanax and you're shooting heroin together, you just get really fucked.

Participants used benzodiazepines in conjunction with opioids to intensify the pleasure of their high as well as to avoid the discomfort of withdrawal or “coming down.” Veronica (25, Female, White), for example, described using benzodiazepines to help her “come down” from the high of other drugs. *“I would make sure that before I even touch the cocaine or the crack...that I had a benzo or an opiate to put, to bring me down.”*

Participants described various risks associated with their use, especially when used in combination with other central nervous system depressants such as opioids or alcohol. Participants discussed heightened risk for benzodiazepine dependence and withdrawal, “black outs,” and, most commonly, overdose, when using benzodiazepines with opioids. Ahmad (22, Male, Latino) described blacking out on benzodiazepines. *“I had one bad experience with that [Xanax]. I took it and then like I don't remember anything for the whole day.”* Others, such as Linda (31, Female, White) talked about dependence on benzodiazepines and how difficult it is for regular users to stop benzodiazepine intake:

“Benzo addiction is bad, the physical addiction, like detoxing off of benzos is really, really hard. It s really physically difficult and very, very nasty.”

Many participants also reported having overdosed when using benzodiazepines in combination with other drugs, particularly opioids. They also reported witnessing other people overdose from this combination or knowing people who died as a result. Some participants overdosed multiple times as a result of mixing benzodiazepines with opioids. For example Jeremy describes one of his multiple overdose experiences: *“...actually that one time when I told you my dad hit me, I think I was on a lot of OxyContin and Xanax, and like I just kind of like went out where he couldn t wake me up... I was eighteen.”* Despite their awareness of the risks associated with their nonmedical benzodiazepine use blacking out, overdosing, and dependence participants continued to use them for their many perceived benefits.

Quantitative Findings

The sample's (n=464) socio-demographic characteristics and opioid use trajectories, with corresponding population estimates, are presented in Table 1. The majority of participants were male, with a mean age of 24.5. Most reported being White/Caucasian, (72%), and a quarter (27%) reported being Latino. Most participants had completed secondary education (80%), and a substantial minority (40%) had attended at least some college. A majority of participants reported growing up in families with incomes of \$51,000 or higher, with 21% reporting household incomes above \$100,000. Nonetheless, 60% reported having experienced homelessness at some point in their lives. Participants' mean age at first nonmedical use of prescription opioids was 16.7 (SD=3.1), and 19.4 (SD=3.5) at first heroin use. A great majority (80%) initiated use of prescription opioids either prior to heroin initiation or within the same year.

Table 2 reports variables related to benzodiazepine use and corresponding population estimates. Most participants (93%) reported lifetime nonmedical use of benzodiazepines, with a mean age at first use of 17.8 (SD=3.2). The majority of the sample (57%) reported regular benzodiazepine use (of those, most reported at least one year of regular use) and (60%) reported nonmedical benzodiazepine use in the past 30 days, averaging ten days of use. About a third of participants reported ever being medically prescribed benzodiazepines, and 44 % reported encouraging fellow drug users to use benzodiazepines as a way to cope with opioid withdrawal.

Bivariate and multivariate associations of lifetime regular nonmedical benzodiazepine use with variables of interest are summarized in Table 3. In bivariate analyses, gender, education and lifetime homelessness were not significantly related to regular use of benzodiazepines. White participants were significantly more likely than non-Whites to engage in regular benzodiazepine use ($OR = 1.77, p < 0.01$), while Latinos were less likely to do so than non-Latinos ($OR = 0.60, p < 0.05$). Compared to participants from families with annual household incomes under \$50,000, participants from higher-income households were more likely to regularly use benzodiazepines. Participants who had used other drugs regularly (heroin, cocaine and prescription stimulants) were more likely to report regular nonmedical benzodiazepine use.

Participants who had ever been treated for anxiety, had ever been medically prescribed benzodiazepines or had ever been in drug treatment had a more than two-fold higher likelihood of reporting regular nonmedical benzodiazepine use. Binging on drugs in the past 30 days and having ever experienced an overdose increased the odds of having regularly used benzodiazepines by 2.57 and 2.32 times, respectively. Participants who reported encouraging fellow drug users to use benzodiazepines as a way to cope with “dope sickness” were 3.23 times as likely to have used benzodiazepines regularly.

In multivariate analysis, the results of which are also reported in Table 3, the following variables remained strongly associated with lifetime regular nonmedical benzodiazepine use: growing up in a middle-income household; having ever overdosed; having ever used cocaine regularly; having ever been medically prescribed benzodiazepines; binging on drugs in the past 30 days; and encouraging others to use benzodiazepines to cope with opioid withdrawal.

Discussion

The results of this mixed methods study reveal a high prevalence of nonmedical benzodiazepine use among young adult opioid users, supporting previous findings (Chen et al., 2011; Havens et al., 2010; Khosla et al., 2011; Lavie, Fatseas, Denis, & Auriacombe, 2009; Toblin et al., 2010) and highlighting the under-acknowledged role of benzodiazepines in the current heightened rates of opioid use in the US. Both qualitative and quantitative findings indicate that benzodiazepine use is very common, and often concurrent with nonmedical prescription opioid and/or heroin use, among young opioid users, with first nonmedical benzodiazepine use occurring soon after first prescription opioid use, during the teenage years. A high proportion of participants in structured interviews reported lifetime nonmedical benzodiazepine use (93%), and 57% reported regular lifetime use. These participants also reported lengthy histories of regular nonmedical benzodiazepine use; for a substantial minority, regular benzodiazepine use can go on for years. This lengthy benzodiazepine use is consistent with other findings (Havens et al., 2010; Rooney et al., 1999) and confirms the significant role of benzodiazepine use in the current opioid epidemic, especially with regard to co-occurring benzodiazepine and opioid use.

Multifunctional Benzodiazepine Use

In addition to the fact that benzodiazepines are reported to be cheaper and more easily accessible in illicit markets than prescription opioids, widespread benzodiazepine use among young opioid users might be further explained by its “multi-functionality” in a context of polysubstance use: enhancing and extending the “high” of prescription opioids or heroin; easing the “come down” from a stimulant high (e.g. cocaine); supplementing use when little or no opioids are available; and managing opioid withdrawal symptoms. Similar findings have been reported elsewhere the literature (Gelkopf et al., 1999; Jones et al., 2012; Lankenau et al., 2012; Liebrezn et al., 2015; O’Brien, 2005; Dwyer, 2005).

“Intrventions” Involving Benzodiazepines

The versatility of benzodiazepines in complementing, supplementing or partially substituting for other drugs might explain the strong correlation between benzodiazepine use and other drug use (heroin, cocaine, and prescription stimulants) found in this study. Versatility might also make benzodiazepines a popular drug to recommend to fellow users (44% of the quantitative sample reported recommending benzodiazepines to others as a way to cope with opioid withdrawal symptoms). We understand such peer recommendations as “intravention” (Friedman et al., 2004) that is, prevention activities that are conducted by and sustained through ongoing actions of members of communities-at-risk. Such “intraventions” serve a health need within the drug-using community, yet recommending benzodiazepines as a way to manage opioid dependence might also lead to unintended negative health consequences such as overdose. Peer-driven prevention efforts should address this risk.

Mental Health Comorbidity

Regular nonmedical use of benzodiazepines was also related to mental health problems, a finding that echoes other research (Gelkopf et al., 1999; Liebrezn et al., 2015), and which suggests that some usage may be explained within a framework of self-medication to help control anxiety. Participants who had ever experienced serious anxiety or been treated for anxiety, as well as those who were ever prescribed benzodiazepines, were more likely to regularly use benzodiazepines nonmedically. Such mental health comorbidity indicates the need to expand mental health services for young opioid users. Further research should explore mechanisms by which drug users resort to self-diagnosis and self-medication to address their mental health needs.

Benzodiazepine use was also associated with being White, having grown up in a middle-income household, engaging in serious forms of drug use (i.e., more likely to use and to inject heroin) and exhibiting riskier drug use (i.e., more likely to inject drugs, report recent “binging” and overdose experience). Other studies also indicate a benzodiazepine-using population that engages in polysubstance use (Kurtz et al., 2011; Tucker et al., 2016) and is largely non-Hispanic White (Chen et al., 2011; McCabe, 2005; McCabe & West, 2014).

Overdose Risk

Participants in qualitative interviews reported experiences of overdose as a result of concomitant use of benzodiazepines with prescription opioids and/or heroin, both personally and among their peers. Bivariate and multivariate results indicate that having ever overdosed was associated with regular nonmedical benzodiazepine use among this group of young adult nonmedical opioid users; this is consistent with the results of Dilokthornsakul et al. (2016) and Dietze et al. (2005) who found that using benzodiazepines in conjunction with opioids at a minimum doubled the risk for overdose. Our findings affirm those of other studies that demonstrate heightened risk for overdose when benzodiazepines are used concurrently with opioids (Chan et al., 2006; Jann et al., 2014; Jones et al., 2015; Kerr et al., 2007; McGregor et al., 1998; Toblin et al., 2010).

Covariates Associated with Regular Nonmedical Benzodiazepine Use

In multivariate analysis, among sociodemographic variables, growing up in a middle-income household remained strongly associated with regular nonmedical benzodiazepine use when controlling for other sets of variables. Among lifetime drug use and mental health variables, having ever overdosed, having ever used cocaine regularly, and having ever been medically prescribed benzodiazepines remained strong predictors of regular nonmedical benzodiazepine use. The association between income and having been medically prescribed benzodiazepines might be explained by the likelihood of young people from middle-income families to have health insurance, thus facilitating access to a doctor who can prescribe benzodiazepines. The association with regular cocaine use is consistent with qualitative findings of polysubstance use among young opioid users and the use of benzodiazepines to “come down” from cocaine high. Lifetime overdose remained strongly associated with regular nonmedical benzodiazepine use confirming the previous research findings reporting an increased overdose risk among those who combine the use of opioids and benzodiazepines. Further research is needed to determine whether young adults’ receipt of prescribed benzodiazepines, experience of overdose and regular cocaine use occurred prior to, during and/or after young adults’ benzodiazepine use. Among post-benzodiazepine use variables, bingeing on drugs in the past 30 days and encouraging others to use benzodiazepines to cope with opioid withdrawal also remained strong correlates of benzodiazepine use.

Limitations

This study has some limitations. Given the structure of recruitment in this study Respondent-Driven Sampling, which is the recruitment of participants by fellow participants traditional inferences about relationships between variables are not valid due to the non-random nature of respondent selection; thus, caution is warranted in interpreting the results of standard bivariate and multivariate tests of association. While the permutation tests used herein are intended to address this limitation and generally confirmed the results of standard bivariate tests for association, multivariate techniques that account for the dependence in RDS data have not yet been developed. Therefore, the results of the multivariate analyses should be treated with particular caution. The RDS-adjusted population estimates presented in Tables 1 and 2 are based on estimators explicitly designed for RDS data, and although there is still some discussion in the literature of which estimator is best in which conditions, the fact that these values are quite close to their sample values in the present study gives further reassurance that there is not undue sensitivity to the specific method of adjustment.

In addition, because of the cross-sectional nature of these data, findings cannot establish causation, although they can demonstrate correlation. Also, because the data are self-reported, they may be susceptible to recall or social desirability bias, especially as drug-use behaviour is particularly socially sensitive. This study focuses exclusively on young adults in New York City who use opioids nonmedically; the results, therefore, may not be generalizable to drug users of other ages or in other areas, particularly those residing in non-urban areas. The study did not include a measure of benzodiazepine dependence or doses used which could be useful in future studies. In terms of the qualitative data, there may have

been participants with different experiences with benzodiazepine use that were not reported in interviews.

In sum, these findings attest to the multifunctionality and widespread use of benzodiazepines among young opioid users, as well as the importance of addressing benzodiazepine use due to its potential to increase risk for overdose. There is a need for treatment efforts to carefully screen for and address dual dependence and concomitant use of benzodiazepines and opioids (Ghitza, Epstein & Preston, 2008; Toblin et al., 2010; White & Irvine, 1999; Wolf, Lavezzi, Sullivan, & Flannagan, 2005). Benzodiazepines, when used alone, rarely lead to death, and it is perhaps this lack of overdose-associated mortality that allows users to view concurrent use of benzodiazepines with other drugs as safe (Mcgregor et al., 1998; Neira-León et al., 2006; Rowe, Santos, Behar & Coffin, 2016). However, when used with other depressant drugs and/or alcohol, benzodiazepines can increase respiratory depression, thereby potentially increasing both the likelihood and lethality of overdose episodes (White et al., 1999).

These findings indicate the need for treatment centres, physicians and harm reduction services to inform users of the risks associated with nonmedical benzodiazepine use, especially when mixed with other substances. However, prevention efforts should go beyond just informing users of such risks, acknowledging the pragmatic reasons (Harris & Rhodes, 2011) for concomitant use, including intensifying the opioid high and coping with withdrawal. Regulatory responses that aim merely at preventing nonmedical access to benzodiazepines (e.g., via prescription drug monitoring programs) without providing viable alternatives for its multiple functions might be counterproductive, possibly leading to riskier behaviour (e.g., in the absence of benzodiazepines, drug users might resort to potentially riskier drugs to manage opioid withdrawal or reduce opioid intake). Data presented in this paper indicate that many young opioid users, despite the heightened risk of overdose, engage in prolonged regular benzodiazepine use while also promoting its use to peers. Such actions are best understood in a context of situated rationality (Rhodes, 1997). As such, the overdose risk associated with benzodiazepine use might be counterweighed by other rationalities of more immediate priority such as enhancing one's high or coping with withdrawal in a situation of limited opioid supply. Young opioid users face multiple risks (e.g. overdose and withdrawal) while addressing competing needs such as staying alive, earning money to sustain adequate opioid intake and avoiding dope sickness. Such risk environments have been shaped by social institutions and shifting policies beyond young drug users' control. Informed by Rhodes' risk environment framework (2009), we should take into account that opioid misuse among today's young adults in the U.S. has occurred in a policy environment that shifted from ample availability of diverted prescription opioids to one of increasingly limited supply. Heavy supply-side initiatives aimed at constraining access to prescription opioids (e.g., restrictive re-classification of specific prescription opioids, heightened law enforcement efforts) have been implemented without a parallel increase in access to opioid substitution therapy. Such a policy shift has left young nonmedical prescription opioid users high and dry; in search of viable alternatives to maintain their opioid supply, many of them have transitioned to heroin use (Mateu-Gelabert et al, 2015; Jones, 2013; Kolodny et al, 2015). Benzodiazepine use may also function in part as a pragmatic response to these structural constraints.

Prevention efforts should take into consideration drug users' risk environments and competing rationalities when addressing benzodiazepine-related harm. Such an approach, acknowledging the limiting structural factors at play, would advise on safer benzodiazepine use while addressing motivations for use and competing priorities within the context of users' social environments. Further research is needed to ground such comprehensive harm prevention approaches to nonmedical benzodiazepine use. Some initiatives that harm reduction efforts might want to consider include: a) emphasize risk reduction through widespread naloxone distribution and call attention to the increased risk for overdose associated with polysubstance use, especially when engaged in alone; b) expand harm reduction education to include messages specifically related to benzodiazepine use (e.g., risks associated with abrupt cessation of benzodiazepine use for users who are physically dependent, differences between benzodiazepine and opioid withdrawal, ways to avoid benzodiazepine dependence, differences between short- and long-acting benzodiazepines); c) offer mental health services uniquely tailored to the needs of opioid users; and d) provide viable alternatives for the drug management functions benzodiazepines serve for many drug users (e.g., facilitate timely access to drug treatment programs and medication-assisted treatment for those who want to reduce or stop drug use).

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References

- Altman DG, Bland JM. How to obtain the P value from a confidence interval. *BMJ*. 2011; 343doi: 10.1136/bmj.d2304
- Ashton H. The diagnosis and management of benzodiazepine dependence. *Current Opinion in Psychiatry*. 2005; 18(3):249–255. [PubMed: 16639148]
- Bachhuber MA, Hennessy S, Cunningham CO, Starrels JL. Increasing benzodiazepine prescriptions and overdose mortality in the United States, 1996–2013. *American Journal of Public Health*. 2016; 106(4):686–688. DOI: 10.2105/AJPH.2016.303061 [PubMed: 26890165]
- Bramness JG, Kornør H. Benzodiazepine prescription for patients in opioid maintenance treatment in Norway. *Drug and alcohol dependence*. 2007; 90(2):203–209. [PubMed: 17478058]
- Braun V, Clarke V. Using thematic analysis in psychology. *Qualitative research in psychology*. 2006; 3(2):77–101.
- Centers for Disease Control and Prevention. Vital Signs: Today's Heroin Epidemic. 2015 Jul 7. Retrieved from <http://www.cdc.gov/vitalsigns/heroin/>
- Chan GM, Stajic M, Marker EK, Hoffman RS, Nelson LS. Testing positive for methadone and either a tricyclic antidepressant or a benzodiazepine is associated with an accidental overdose death: analysis of medical examiner data. *Academic Emergency Medicine*. 2006; 13(5):543–547. [PubMed: 16641481]
- Chen KW, Berger CC, Forde DP, D'Adamo C, Weintraub E, Gandhi D. Benzodiazepine use and misuse among patients in a methadone program. *BMC Psychiatry*. 2011; 11(90)
- Coben JH, Davis SM, Furbie PM, Sikora RD, Tillotson RD, Bossarte RM. Hospitalizations for poisoning by prescription opioids, sedatives, and tranquilizers. *American Journal of Preventive Medicine*. 2010; 38(5):517–524. [PubMed: 20409500]

- Darke S, Ross J, Mills K, Teesson M, Williamson A, Havard A. Benzodiazepine use among heroin users: Baseline use, current use and clinical outcome. *Drug and Alcohol Review*. 2010; 29(3):250–255. [PubMed: 20565516]
- Darke S, Ross J, Teesson M, Lynskey M. Health service utilization and benzodiazepine use among heroin users: Findings from the Australian Treatment Outcome Study (ATOS). *Addiction*. 2003; 98(8):1129–1135. [PubMed: 12873247]
- Dietze P, Jolley D, Fry C, Bammer G. Transient changes in behaviour lead to heroin overdose: results from a case-crossover study of non-fatal overdose. *Addiction*. 2005; 100(5):636–642. [PubMed: 15847621]
- Dilokthornsakul P, Moore G, Campbell JD, Lodge R, Traugott C, Zerzan J, Allen R, Page RL 2nd. Risk factors of prescription opioid overdose among Colorado Medicaid beneficiaries. *Journal of Pain*. 2016; 17(4):436–43. [PubMed: 26721613]
- Dwyer, Robyn. Privileging pleasure: Temazepam injection in a heroin marketplace. *International Journal of Drug Policy*. 2008; 19(5):367–374. [PubMed: 17997090]
- Evans JL, Hahn JA, Lum PJ, Stein ES, Page K. Predictors of injection drug use cessation and relapse in a prospective cohort of young injection drug users in San Francisco, CA (UFO Study). *Drug and Alcohol Dependence*. 2009; 101(3):152–157. [PubMed: 19181458]
- Frank D, Mateu-Gelabert P, Guarino H, Bennett A, Wendel T, Jessell L, Teper A. High risk and little knowledge: Overdose experiences and knowledge among young adult nonmedical prescription opioid users. *International Journal of Drug Policy*. 2015; 26(1):84–91. [PubMed: 25151334]
- Forsyth AJ, Farquhar D, Gemmell M, Shewan D, Davies JB. The dual use of opioids and temazepam by drug injectors in Glasgow (Scotland). *Drug and alcohol dependence*. 1993; 32(3):277–280. [PubMed: 8348877]
- Friedman SR, Maslow C, Bolyard M, Sandoval M, Mateu-Gelabert P, Neaigus A. Urging others to be healthy: “Intravention” by injection drug users as a community prevention goal. *AIDS Education and Prevention*. 2004; 16(3):250–263. [PubMed: 15237054]
- Fry CL, Bruno RB. Recent trends in benzodiazepine use by injecting drug users in Victoria and Tasmania. *Drug and Alcohol Review*. 2002; 21(4):363–367. [PubMed: 12537706]
- Gelkopf M, Bleich A, Hayward R, Bodner G, Adelson M. Characteristics of benzodiazepine abuse in methadone maintenance treatment patients: A 1 year prospective study in an Israeli clinic. *Drug and Alcohol Dependence*. 1999; 55(1–2):63–68. [PubMed: 10402150]
- Ghitza UE, Epstein DH, Preston KL. Self-report of illicit benzodiazepine use on the Addiction Severity Index predicts treatment outcome. *Drug and Alcohol Dependence*. 2008; 97(1–2):150–157. [PubMed: 18499354]
- Gile K. Improved inference for Respondent-Driven Sampling data with application to HIV prevalence estimation. *Journal of the American Statistical Association*. 2011; 106(498):135–146.
- Häkkinen M, Launiainen T, Vuori E, Ojanperä I. Benzodiazepines and alcohol are associated with cases of fatal buprenorphine poisoning. *European Journal of Clinical Pharmacology*. 2012; 68(3):301–309. [PubMed: 21927835]
- Harris M, Rhodes T. Venous access and care: harnessing pragmatics in harm reduction for people who inject drugs. *Addiction*. 2012; 107(6):1090–1096. [PubMed: 22151433]
- Handcock, MS., Fellows, IE., Gile, KJ. RDS: Respondent-Driven Sampling, version 0.7. 2012. <http://CRAN.R-project.org/package=RDS>
- Havens JR, Walker R, Leukefeld CG. Benzodiazepine use among rural prescription opioids users in a community-based study. *Journal of Addiction Medicine*. 2010; 4(3):137–139. [PubMed: 21769029]
- Heckathorn DD. Respondent-driven sampling: A new approach to the study of hidden populations. *Social Problems*. 1997; 44(2):174–199.
- Heckathorn DD, Semaan S, Broadhead RS, Hughes JJ. Extensions of respondent-driven sampling: A new approach to the study of injection drug users aged 18–25. *AIDS and Behaviour*. 2002; 6(1):55–67.
- Jann M, Kennedy WK, Lopez G. Benzodiazepines a major component in unintentional prescription drug overdoses with opioid analgesics. *Journal of pharmacy practice*. 2014; 27(1):5–16. [PubMed: 24436437]

- Jessell L, Mateu-Gelabert P, Guarino H, Vakharia SP, Syckes C, Goodbody E, Friedman S. Sexual violence in the context of drug use among young adult opioid users in New York City. *Journal of Interpersonal Violence*. 2015
- Jones CM. Heroin use and heroin use risk behaviors among nonmedical users of prescription opioid pain relievers United States, 2002 2004 and 2008 2010. *Drug and alcohol dependence*. 2013; 132(1):95–100. [PubMed: 23410617]
- Jones CM, Logan J, Gladden RM, Bohm MK. Vital signs: demographic and substance use trends among heroin users United States, 2002 2013. *Morbidity and Mortality Weekly Report*. 2015; 64(26):719–725. [PubMed: 26158353]
- Jones CM, McAninch JK. Emergency department visits and overdose deaths from combined use of opioids and benzodiazepines. *American Journal of Preventive Medicine*. 2015; 49(4):493–501. [PubMed: 26143953]
- Jones JD, Mogali S, Comer SD. Polydrug abuse: A review of opioid and benzodiazepine combination use. *Drug and Alcohol Dependence*. 2012; 125(1–2):8–18. [PubMed: 22857878]
- Kerr T, Fairbairn N, Tyndall M, Marsh D, Li K, Montaner J, Wood E. Predictors of non-fatal overdose among a cohort of polysubstance-using injection drug users. *Drug and Alcohol Dependence*. 2007; 87(1):39–45. [PubMed: 16959438]
- Khosla N, Juon HS, Kirk GD, Astemborski J, Mehta SH. Correlates of non- medical prescription drug use among a cohort of injection drug users in Baltimore City. *Addictive Behaviours*. 2011; 36(12):1282–1287.
- Kim D, Gile K, Guarino H, Mateu-Gelabert P. Inferring Bivariate Associations for Respondent- Driven Sampling Data. 2016 Manuscript in preparation.
- Kolodny A, Courtwright DT, Hwang CS, Kreiner P, Eadie JL, Clark TW, Alexander GC. The prescription opioid and heroin crisis: a public health approach to an epidemic of addiction. *Annual review of public health*. 2015; 36:559–574.
- Kurtz SP, Surratt HL, Levi-Minzi MA, Mooss A. Benzodiazepine dependence among multidrug users in the club scene. *Drug and Alcohol Dependence*. 2011; 119(1–2):99–105. [PubMed: 21708434]
- Lankenau SE, Teti M, Silva K, Bloom JJ, Harocopos A, Treese M. Patterns of prescription drug misuse among young injection drug users. *Journal of Urban Health*. 2012; 89(6):1004–1016. [PubMed: 22684424]
- Lavelle TL, Hammersley R, Forsyth A, Bain D. The use of buprenorphine and temazepam by drug injectors. *Journal of addictive diseases*. 1991; 10(3):5–14. [PubMed: 1932153]
- Lavie E, Fatséas M, Denis C, Auriacombe M. Benzodiazepine use among opiate-dependent subjects in buprenorphine maintenance treatment: Correlates of use, abuse and dependence. *Drug and Alcohol Dependence*. 2009; 99(1–3):338–344. [PubMed: 18824311]
- Liebrezn M, Schneider M, Buadze A, Gehring MT, Dube A, Caflisch C. High-dose benzodiazepine dependence: A qualitative study of patients' perceptions on initiation, reasons for use, and obtainment. *PLOS ONE*. 2015; 10(11)
- Longo LP, Johnson B. Addiction: Part I. Benzodiazepines side effects, abuse risk and alternatives. *American Family Physician*. 2000; 61(7):2121–2128. [PubMed: 10779253]
- Mateu-Gelabert P, Guarino H, Jessell L, Teper A. Injection and sexual HIV/HCV risk behaviours associated with nonmedical use of prescription opioids among young adults in New York City. *Journal of Substance Abuse Treatment*. 2015; 48(1):13–20. [PubMed: 25124258]
- McCabe SE. Correlates of nonmedical use of prescription benzodiazepine anxiolytics: results from a national survey of U.S. college students. *Drug and Alcohol Dependence*. 2005; 79(1):53–62. [PubMed: 15943944]
- McCabe SE, West BT. Medical and nonmedical use of prescription benzodiazepine anxiolytics among U.S. high school seniors. *Addictive Behaviours*. 2014; 39(5):959–964.
- McGregor C, Darke S, Ali R, Christie P. Experience of non-fatal overdose among heroin users in Adelaide, Australia: Circumstances and risk perceptions. *Addiction*. 1998; 93(5):701–711. [PubMed: 9692269]
- McKnight C, Des Jarlais D, Bramson H, Tower L, Abdul-Quader AS, Nemeth C, Heckathorn D. Respondent-driven sampling in a study of drug users in New York City: notes from the field. *Journal of Urban Health*. 2006; 83(6 Suppl):i54–i59. [PubMed: 16977493]

- National Institute on Drug Abuse. Research Report Series: Prescription Drug Abuse. 2014 Nov. Retrieved from https://www.drugabuse.gov/sites/default/files/prescriptiondrugrrs_11_14.pdf
- Neira-León M, Barrio G, Brugal MT, de la Fuente L, Ballesta R, Bravo MJ, Silva TC, Rodríguez-Martos A. Project Itinere Group. Do young heroin users in Madrid, Barcelona and Seville have sufficient knowledge of the risk factors for unintentional opioid overdose? *Journal of Urban Health*. 2006; 83(3):477–496. [PubMed: 16739049]
- O'Brien CP. Benzodiazepine use, abuse and dependence. *Journal of Clinical Psychiatry*. 2005; 66(Suppl 2):28–33.
- Oliver P, Keen J. Concomitant drugs of misuse and drug using behaviours associated with fatal opiate-related poisonings in Sheffield, UK, 1997–2000. *Addiction*. 2003; 98(2):191–197. [PubMed: 12534424]
- Paone, D., Tuazon, E., Nolan, M., Mantha, S. Unintentional drug poisoning (overdose) deaths involving opioids in New York City, 2000–2014. New York City: Department of Health and Mental Hygiene Epi Data Brief; 2015. p. 66 Updated March 2016
- Patton, MQ. Qualitative research and evaluation methods. 3. Thousand Oaks, CA: Sage Publications; 2002.
- Perret G, Déglon JJ, Kreek MJ, Ho A, La Harpe R. Lethal methadone intoxications in Geneva, Switzerland, from 1994 to 1998. *Addiction*. 2000; 95(11):1647–1653. [PubMed: 11219368]
- Puntillo K, Casella V, Reid M. Opioid and benzodiazepine tolerance and dependence: application of theory to critical care practice. *Heart & Lung: The Journal of Acute and Critical Care*. 1997; 26(4):317–324. [PubMed: 9257142]
- R Core Team. R: A Language and Environment for Statistical Computing. Vienna, Austria: 2015. <https://www.R-project.org>
- Rhodes T. Risk environments and drug harms: a social science for harm reduction approach. *International Journal of Drug Policy*. 2009; 20:193–201. [PubMed: 19147339]
- Rhodes T. Risk theory in epidemic times: sex, drugs and the social organization of 'risk behavior'. *Sociology of Health & Illness*. 1997; 19(2):208–27.
- Rooney S, Kelly G, Bamford L, Sloan D, O'Connor JJ. Co-abuse of opiates and benzodiazepines. *Irish Journal of Medical Science*. 1999; 168(1):36–41. [PubMed: 10098342]
- Ross J, Darke S, Hall W. Benzodiazepine use among heroin users in Sydney: patterns of use, availability and procurement. *Drug and Alcohol Review*. 1996; 15(3):237–43. [PubMed: 16203378]
- Rowe C, Santos GM, Behar E, Coffin PO. Correlates of overdose risk perception among illicit opioid users. *Drug & Alcohol Dependence*. 2016; 159:234–239. [PubMed: 26754425]
- Smith A, Tett S, Hall W. The contribution of injecting drug users in Sydney, Melbourne and Brisbane to rising benzodiazepine use in Australia 2000 to 2006. *Australian and New Zealand journal of public health*. 2010; 34(3):315–319. [PubMed: 20618276]
- Strang J, Griffiths P, Abbey J, Gossop M. Survey of use of injected benzodiazepines among drug users in Britain. *BMJ*. 1994; 308(6936):1082. [PubMed: 8173431]
- Substance Abuse and Mental Health Services Administration, Center for Behavioural Health Statistics and Quality. The DAWN report: Benzodiazepines in combination with opioid pain relievers or alcohol: greater risk of more serious ED visit outcomes. Rockville, MD: Dec 18. 2014
- Substance Abuse and Mental Health Services Administration, Center for Behavioural Health Statistics and Quality. The TEDS report: Admissions reporting benzodiazepine and narcotic pain reliever abuse at treatment entry. Rockville, MD: Dec 13. 2012
- Substance Abuse and Mental Health Services Administration, Center for Behavioural Health Statistics and Quality. The TEDS report: Substance abuse treatment admissions for abuse of benzodiazepines. Rockville, MD: Jun 2. 2011
- Substance Abuse and Mental Health Services Administration (SAMHSA). Results from the 2010 National Survey on Drug Use and Health: Summary of National Findings, NSDUH Series H-41, HHS Publication No. (SMA) 11-4658. Rockville, MD: 2011.
- Toblin RL, Paulozzi LJ, Logan JE, Hall AJ, Kaplan JA. Mental illness and psychotropic drug use among prescription drug overdose deaths: a medical examiner chart review. *Journal of Clinical Psychiatry*. 2010; 71(4):491–496. [PubMed: 20409446]

- Tucker D, Hayashi K, Milloy MJ, Nolan S, Dong H, Kerr T, Wood E. Risk factors associated with benzodiazepine use among people who inject drugs in an urban Canadian setting. *Addictive Behaviours*. 2016; 52:103–107.
- Ward M, Barry J. Opiate-related deaths in Dublin. *Irish Journal of Medical Science*. 2001; 170(1):35–7. [PubMed: 11440410]
- White J, Irvine RJ. Mechanisms of fatal opioid overdose. *Addiction*. 1999; 94(7):961–972. [PubMed: 10707430]
- Wolf BC, Lavezzi WA, Sullivan LM, Flannagan LM. One hundred seventy two deaths involving the use of oxycodone in Palm Beach County. *Journal of Forensic Sciences*. 2005; 50(1):192–195. [PubMed: 15831018]
- Wunsch MJ, Nakamoto K, Behonick G, Massello W. Opioid deaths in rural Virginia: A description of the high prevalence of accidental fatalities involving prescribed medications. *The American Journal on Addictions*. 2009; 18(1):5–14. [PubMed: 19219660]

Table 1

Participant Characteristics (n = 464)

Characteristic	Sample Mean(SD)	Sample n (%)	Population Estimate
<i>Age</i>	24.5 (3.2)		
<i>Gender</i>			
Female		153 (33)	34 (4.1)
Male		307 (66)	65 (4.1)
Transgender		4 (1)	0.3 (0.2)
<i>Race</i>			
American Indian/Native Alaskan		6 (1)	1 (0.7)
Asian		6 (1)	2 (1.3)
African American		18 (4)	3 (1.8)
White		335 (72)	75 (4.3)
Multiracial		46 (10)	9 (2.3)
Missing ^I		52 (11)	--
<i>Ethnicity</i>			
Latino		124 (27)	25 (4.3)
<i>Education</i>			
Did not complete H.S.		92 (20)	18 (4.0)
H.S. Graduate/GED		186 (40)	34 (4.3)
Some College		161 (35)	38 (4.4)
College Graduate or more		24 (5)	9 (3.3)
<i>Household income while growing up</i>			
\$0–\$50,000		186 (40)	40 (4.3)
\$51,000–\$100,000		149 (32)	31 (4.4)
\$101,000+		96 (21)	22 (4.0)
Don't Know		32 (7)	--
<i>Ever Homeless</i>		279 (60)	53.7 (4.4)
<i>Never used prescription opioids</i>		5 (1)	1.3 (1.4)
<i>Never used heroin</i>		56 (12)	10 (3.5)
<i>Opioid Use Trajectory</i>			
Used heroin before POs		89 (19)	17.9 (4.3)
Used POs before heroin		312 (67)	66.4 (5.1)
Used heroin and POs in the same year		62 (13)	15.4 (3.6)

^I Most missing values for race are due to Latinos who identified their race, as well as their ethnicity, as Latino and, because Latino was not a response option for race, opted to leave this item blank.

Table 2

Benzodiazepine Use and Other Benzodiazepine-related Variables (n = 464)

Variable	Sample n (%)	Population Estimate % (SE)
<i>Nonmedical Benzodiazepine Use (lifetime)</i>		
Never used benzos	33 (7)	9.9% (0.04)
Sporadic-Not regular use	167 (36)	31.5% (0.05)
Less than one year regular ¹ use	105 (23)	22.1% (0.04)
1–2 years regular use	69 (15)	16.3 (0.04)
3–5 years regular use	60 (13)	13.7% (0.03)
6 years or more regular use	29 (6)	6.3% (0.02)
<i>Nonmedical Benzodiazepine Use (past 30 days)</i>	277 (60)	60.9% (0.05)
<i>Number of days used benzodiazepines nonmedically (past 30 days, n = 277)²</i>	<i>M = 9.8, SD = 9.9</i>	
1–4 days	121 (44)	--
5–10 days	65 (24)	--
11–28 days	54 (20)	--
Every day	37 (13)	--
<i>Ever experienced serious anxiety or tension</i>	332 (72)	70.9% (0.05)
<i>Ever treated for anxiety or tension</i>	174 (38)	43.6 (0.06)
<i>Ever medically prescribed benzodiazepines</i>	141 (30)	38.0% (0.05)
<i>Encouraged others to use benzodiazepines as a way to cope with “dope sickness”</i>	202 (44)	47.4% (0.06)

¹“Regular” benzodiazepine use is defined as three or more times per week.

²For this variable, frequencies are based on the sample subset that used benzodiazepines in the past 30 days (n=277). No population estimates were generated for this variable.

Table 3

Correlates of Lifetime Regular Nonmedical Benzodiazepine Use

	No n (%) 201 (43.3)	Yes n (%) 263 (56.7)	OR	standard p-value	Regular ¹ Benzo Use Permutation Test ² p-value	Adjusted OR	Adjusted CI 95%	Adjusted p-value
Gender								
Male	139 (69)	168 (64)	0.76	0.172	0.1774			
Female	59 (29)	94 (36)	1.32	0.172				
Race								
White	132 (66)	203 (77)	1.77	<0.01	<0.05			
Non-White	69 (34)	60 (23)						
Ethnicity								
Latino	65 (32)	59 (22)	0.60	<0.05	<0.05			
Non-Latino	134 (67)	204 (78)						
Education								
Did not complete high school	39 (19)	53 (20)	--	--	0.1298			
High school graduate/GED	97 (48)	89 (34)	0.68	0.13				
Some college or more	64 (32)	121 (46)	1.39	0.21	0.205			
Household Income								
Growing Up (annual)								
\$0–\$50,000	99 (49)	87 (33)	--					
\$51,000–\$100,000	49 (24)	100 (38)	2.32	<0.001	<0.001	1.833	1.114–3.037	0.018
\$101,000 or more	37 (18)	59 (22)	1.81	<0.05	<0.05	1.132	0.633–2.025	0.689
Homelessness (lifetime)								
Yes	112 (56)	167 (64)	1.38	0.0917	0.0958			
No	89 (44)	96 (36)						
Regular Heroin Use (lifetime)								
Yes	158 (79)	238 (90)	2.59	<0.001	<0.05			
No	43 (21)	25 (10)						
Regular Nonmedical Prescription Stimulant Use (lifetime)								
Yes	34 (17)	70 (27)	1.78	<0.05	<0.05			

	Regular ¹ Benzo Use					
	No n (%)	Yes n (%)	OR	standard p-value	Permutation Test ² p-value	Adjusted OR
	201 (43.3)	263 (56.7)				Adjusted CI 95%
						Adjusted p-value
No	167 (83)	193 (73)				
Regular Cocaine Use (lifetime)						
Yes	65 (32)	141 (54)	2.42	<0.0001	<0.001	1.587
No	136 (68)	122 (46)				1.001–2.521
0.050						
Regular Heroin Injection (lifetime)						
Yes	109 (54)	187 (71)	2.08	<0.001	<0.001	
No	92 (46)	76 (29)				
Experienced serious anxiety or tension (lifetime)						
Yes	119 (59)	213 (81)	2.94	<0.0001	<0.001	1.513
No	82 (41)	50 (19)				0.909–2.521
0.111						
Treated for anxiety or tension (lifetime)						
Yes	52 (26)	122 (46)	2.48	<0.0001	<0.001	
No	149 (74)	141 (54)				
Prescribed benzodiazepines(lifetime)						
Yes	84 (42)	89 (34)	2.72	<0.0001	<0.001	2.003
No	117 (58)	174 (66)				1.203–3.365
0.008						
Participation In Drug Treatment (lifetime)						
Yes	129 (64)	217 (83)	2.63	<0.0001	<0.001	
No	72 (36)	46 (17)				
Binged on Drugs (last 30 days)						
Yes	122 (61)	210 (80)	2.57	<0.0001	<0.001	2.561
No	79 (39)	53 (20)				1.580–4.191
0.000						
Experienced Overdose (Lifetime)						
Yes	72 (36)	146 (56)	2.32	<0.0001	<0.001	1.713
No	127 (63)	111 (42)				1.081–2.717
0.022						
Used Benzodiazepines at Last Overdose						
Yes	71 (35)	146 (56)	2.28	<0.0001	<0.001	
No	130 (65)	117 (44)				
Encouraged Others to Use Benzodiazepines to Cope with “Dopesickness” (Lifetime)						

	Regular ¹ Benzo Use					Adjusted OR	Adjusted CI 95%	Adjusted p-value
	No n (%)	Yes n (%)	OR	standard p-value	Permutation Test ² p-value			
Yes	201 (43.3)	263 (56.7)	3.23	<0.0001	<0.001	2.104	1.333–3.334	0.002
No	145 (72)	117 (44)						

¹“Regular” benzodiazepine use is defined as three or more times per week.

²Permutation tests were conducted in order to account for the dependence inherent in RDS data.