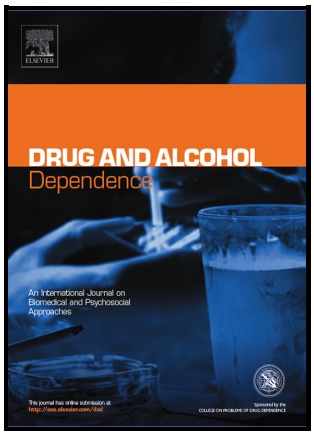

Correlates of Recent Overdose among People Who Inject Drugs in the San Diego/Tijuana Border Region

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Abstract

Background. Along the Mexico-US border, illicitly manufactured fentanyls (fentanyl) have been detected in other illicit drugs, including street opioid formulations known as 'china white.' We studied correlates of recent overdose among people who inject drugs (PWID), focusing on the risk of knowlingly or unknowingly using fentanyl in china white.

Methods. From October 2020 - September, 2021 we surveyed participants in San Diego, California and Tijuana, Mexico and employed Poisson regression to identify correlates of recent overdose.

Results. Of 612 PWID, most were male (74.0%), Latinx (71.9%), US residents (67.0%). Mean age was 43 years. In the last six months, 15.8% experienced overdose, 31.0% knowingly used fentanyl and 11.1% used china white, of whom 77.9% did not think it contained fentanyl. After controlling for sex and race, factors independently associated with risk of overdose included knowingly using fentanyl, using china white and not believing it contained fentanyl, recent drug rehabilitation, being stopped/arrested by police, and homelessness. Further, PWID who believed china white contained fentanyl were less likely to use it.

Conclusions: Both intentional fentanyl use and unintentional exposure to fentanyl via china white were associated with overdose risk; however, PWID who believed china white contained fentanyl were less likely to use it. These data suggest that advanced drug checking systems should be implemented to empower PWID to avoid dangerous street formulations or to plan their drug use knowing its contents. Other overdose risk factors such as decreased tolerance following drug treatment, police interactions, and homelessness also require urgent intervention.

Keywords: fentanyl, overdose, injection drug use, Tijuana, San Diego, US-Mexico border

1.1 Introduction

North America is experiencing an increasingly deadly overdose crisis, with U.S. fatal overdoses surpassing 100,000 in 2021 (Centers for Disease Control and Prevention, 2022). Illicitly manufactured synthetic fentanyls (fentanyl) has become more prevalent in the illicit drug supply due to its relative potency and profitability for traffickers (Mars et al., 2019; Pardo and Reuter, 2020). Fentanyl is a full agonist of the μ-opioid receptors, activation of which leads to respiratory and central nervous system depression (Armenian et al., 2018). Given its high potency and that its concentration in a given drug sample is often unknown, fentanyl has been associated with increased overdose risk (Park et al., 2018; Shrestha et al., 2021). Since its introduction in North America and broad contamination of the illicit opioid supply (Ciccarone, 2017; Tobias et al., 2022), some opioid consumers now actively seek fentanyl, in part due to increased tolerance leading to a preference for more potent opioids (Ickowicz et al., 2022; Mazhnaya et al., 2020; Morales et al., 2019; Urmanche et al., 2022). However, some people who use drugs (PWUD) prefer to avoid fentanyl (Betsos et al., 2021; Carroll et al., 2017), although they have limited means for detecting its presence.

Although causal relationships have not been established, unintentional fentanyl use may put PWUD at even greater risk of overdose as they do not anticipate its presence and cannot alter drug use behaviors accordingly. Case reports have detailed unexpected overdose and deaths associated with use of fentanyl-contaminated drugs (Armenian et al., 2019; Khatri et al., 2018). In North America, fentanyl has been found

(or suspected following an unexpected overdose) in heroin, pressed pills imitating prescription opioids, methamphetamine, cocaine, and benzodiazepines (DiSalvo et al., 2021; Green et al., 2020; Meacham et al., 2020; Park et al., 2021; Tobias et al., 2022; Tupper et al., 2018).

Mexican criminal organizations are now the primary source of the fentanyl in the U.S. (Drug Enforcement Administration, 2020). Many U.S. cities along the Mexican border, including San Diego, California bordering Tijuana, Baja California, Mexico, are considered high intensity drug-trafficking areas by the Drug Enforcement Administration (Drug Enforcement Administration, 2021) where fentanyl has become increasingly common (Fleiz et al., 2020; Friedman et al., 2022a). San Diego and Tijuana are neighboring cities divided by the busiest land border crossing in the U.S. with populations approximately 1.5 and 2 million, respectively. In San Diego, drug overdose rates have steadily increased over time, with a marked opioid-related death rate surge of 70% between 2019 and 2020 largely due to fentanyl (California Department of Public Health, n.d.). Notably, it is unknown whether fatal fentanyl-related overdoses in California were due to intentional use or contamination of the drug supply. Drug surveillance and overdose data is limited in Mexico, but PWUD in Tijuana are likely similarly affected by the ubiquity of fentanyl (Fleiz et al., 2020; Friedman et al., 2022a). One 2018 study among people who inject drugs (PWID) in Tijuana found that 54% had ever experienced an opioid-related overdose (Rafful et al., n.d.).

In a recent ethnographic study with PWUD in Tijuana, informants reported greater prevalence, potency, and perceived overdose threat associated with china white, a powder heroin formulation found to contain fentanyl (Friedman et al., 2022a). Although china white has been described as a synthetic opioid associated with overdose (Ayres et al., 1981; Martin et al., 1991), it is not clear to what extent people who use it identify the substance as such. However, a recent study in Tijuana reported that, unbeknownst to PWID in the study, 55 of 59 (93%) of china white samples contained fentanyl (Fleiz et al., 2020). PWUD who are unaware of the contents of their drug supply may underestimate their overdose risk.

It is important to track fentanyl and overdose trends in the U.S.-Mexico border region as there are public health implications of cross-border drug use (Horyniak et al., 2017; Wagner et al., 2012). Between 15% - 54% of PWID in San Diego report going to Mexico to use drugs (Horyniak et al., 2017; Volkmann et al., 2012; Wagner et al., 2012) due to easier access to drugs that are perceived to be less expensive and better quality (Wagner et al., 2012). As an additional potential pull factor for cross-border drug use, Mexico decriminalized possession of small quantities of drugs for personal use in 2009 (NOM-028-SSA2-2009, 2009).

We assessed correlates of recent overdose among PWID in the San Diego-Tijuana border region, hypothesizing that use of china white would increase the risk of overdose, and that participants that used china white but did not believe it contains fentanyl were at higher risk of overdose. We also anticipated that cross-border drug use among PWID in San Diego would be associated with increased overdose risk due to less familiarity with the drug supply in Tijuana and greater exposure to fentanyl. This

study has implications for overdose prevention and outreach initiatives among PWUD who may knowingly or unknowingly use fentanyl.

1.2. Materials and Methods

1.2.1 Participants

We utilized baseline survey data collected in a longitudinal cohort study of 612 PWID in the San Diego-Tijuana region aimed at collecting information about HIV, HCV, overdose, drug use trends, and the drug market as described elsewhere (Strathdee et al., 2021). In the cohort study, trained interviewers used a short screener to identify eligible participants between October 2020 and September 2021. Inclusion criteria were being aged 18 or older, speaking English or Spanish, reporting past-month injection drug use (as evidenced through injection stigmata), and living in San Diego or Tijuana. San Diego participants were purposively sampled such that half (n=200 of 400) reported cross-border drug use (e.g. were PWID who live in San Diego but injected drugs in Mexico within the two years prior), while the other half did not.

Interviewers recruited participants in various locations around both cities including on the street, parks, shelters, motels, river canyons, encampments, and vacant lots. Following screening, eligible participants provided written informed consent and underwent computer assisted interviewer-administered surveys.

1.2.2 Survey measures and data collection

Participants reported sociodemographics; lifetime and past 6-month overdose experiences; interactions with law enforcement (i.e. being stopped or arrested); housing/living situations; hours per day spent in the street; and enrollments in a drug/alcohol rehabilitation center. Participants were also asked about lifetime and past 6-month use of illicit substances including heroin, oxycontin, prescription opioids, cocaine, methamphetamine, china white, fentanyl, PCP/Angel dust, ecstasy, ketamine, other hallucinogens, inhalants, tranquilizers, and barbiturates. Drug use referred to any method reported (e.g., injecting, smoking, inhaling, etc.) and participants were asked about use of each specific drug one-by-one. Importantly, participants may have used some drugs unknowingly and thus did not report their use. Participants were also asked whether they had injected certain opioid and stimulant combinations, including heroin and cocaine (i.e., speedballs), heroin and crystal meth, china white and crystal meth, and fentanyl and crystal meth. Given our survey only included questions about these specific combinations, our polysubstance injection variable is likely a conservative estimate of polysubstance use. Overdose was defined as “a situation where you passed out, could not wake up, *or* your lips turned blue” following drug use.

Due to recent reports of increasing china white availability in the border region through formative research with PWID, participants were also asked, “What type(s) of drugs do you think are in china white?” to which respondents could reply any combination of the following: heroin, fentanyl, oxycontin, prescription opioids, methamphetamine, cocaine, crocodile/krokodil, barbiturates, cutting agents (e.g., baking

soda, powdered milk, caffeine, etc.), poison, or other. When respondents replied with "other," their responses were recorded in an open-ended field.

The survey was translated into Spanish, back-translated into English, and verified for accuracy by bilingual team members. Participants received $20 USD as compensation. Study protocols were approved by the Human Research Protections Program and Biosafety Committee at the University of California San Diego (UCSD) and the institutional review board at Xochicalco University.

1.2.3 Statistical analysis

The outcome was a binary variable reflecting self-reported overdose in the past six months from baseline interviews. Participant characteristics were compared between those who experienced an overdose and those who did not using T-tests for continuous variables and Chi-square tests or Fisher's exact tests for categorical variables.

We performed robust univariate and multivariate Poisson regressions (Chen et al., 2018) to identify factors associated with risk of overdose. We examined each drug or drug combination used in the past six months by more than 5% of the total sample. Additionally, to assess the relationship between overdose and unknowingly using fentanyl via china white, we created a categorical variable indicating whether participants used china white and, if they did, whether they believed it contained fentanyl. We also assessed the association between the risk of overdose and sex, age, and race/ethnicity as well as past six-month homelessness, law enforcement interactions (being stopped/arrested by police), enrollment in a drug/alcohol rehabilitation center, and among San Diego residents, cross-border drug use. Participants who reported that they had been in a place where they "went and stayed for help with drug or alcohol problems" in the last six months were considered to have been enrolled in a drug/alcohol rehabilitation center. A participant was considered to be experiencing homelessness in the last six months if they reported mostly sleeping in a shelter/welfare residence, workplace, rented room, vehicle, abandoned building, deportee shelter, on the streets, or in a shooting gallery.

Variables independently attaining <=5% significance in univariate models were considered for inclusion in multivariate models. Race and sex were used as covariates in the multivariable models, regardless of their significance. We assessed all potential interactions between variables in the final model and checked for multi-collinearity using variance inflation factors and condition index diagnostics. Significant interactions were further explored graphically and analytically by calculating the simple main effects of the corresponding variables on the outcome.

In an additional exploratory analysis, we conducted a logistic regression to discern the association between believing china white contains fentanyl and the binary outcome of using china white in the past six months.

1.3 Results

1.3.1 Study sample characteristics

As displayed in Table 1, of 612 PWID, most were male (74.0%), Latinx (71.9%), unmarried or not in a common-law marriage (81.0%), U.S. residents (67.0%) with a mean age of 43 years (SD: 10.8). More than half (52.0%) reported any prior overdose of whom 15.8% reported an overdose in the past six months. In the past six months, 31.0% reported having been stopped or arrested by police, only 3.9% had been enrolled in a drug/alcohol rehabilitation center, and 21.6% had experienced homelessness.

Heroin (79.1%) followed by methamphetamine (75.3%) were the most commonly used substances. Past six-month fentanyl use was reported by 31.0% of participants and 18.1% indicated past six-month use of china white. Participants reported injecting drugs an average of 2.36 (SD: 1.53) times per day and over half (56.2%) reported polysubstance injection.

To further investigate participants' beliefs about the contents of china white, we calculated responses to this survey question among the entire sample, regardless of whether they had recently used it (Figure 1). Potential responses were not mutually exclusive. "Other" responses were recoded if they fit one of the provided categories. Overall, less than half of participants (40.0%) considered china white to contain fentanyl or another synthetic opioid, followed by 33.2% who believed it contained heroin, and 16.0% who believed it contained methamphetamine. Importantly, as shown in Table 1, among those who used china white (n=68), 53 (77.9%) did not identify its contents as fentanyl or another synthetic opioid.

1.3.2 Group comparisons

Table 1 shows that relative to those who did not recently overdose, PWID who did were significantly more likely to be White (50.5% versus 33.2%, p=0.002) and non-Hispanic/Latinx/Mexican (62.9% versus 73.6%, p=0.04), experience homelessness (45.4% versus 17.1%, p<0.001), spend more hours per day on the street (mean: 18.2 versus 15.1 hours, p<0.001), report being recently stopped or arrested by police (44.3% versus 28.5%, p=0.003), and have been recently enrolled in a drug/alcohol rehabilitation center (14.4% versus 1.9%, p<0.001).

1.3.3 Substance use

Participants who reported past six-month overdose were significantly more likely to report use of heroin (p=0.008), fentanyl (p<0.001), oxycontin (p=0.024), china white (p<0.001), cocaine (p=0.001), speedballs (p<0.001), methamphetamine (p=0.002), and PCP/angel dust (p<0.001) relative to those who did not experience a recent overdose (Table 1). Those who overdosed reported greater average daily injection drug use (p=0.002) and were more likely to engage in polysubstance injection (p<0.001). People who used china white were significantly more likely to experience recent overdose, regardless of whether they believed it contained fentanyl.

1.3.4 Univariate analysis

As shown in Table 2, identifying as White relative to non-White was associated with greater risk of past six-month overdose (Risk Rate Ratio (RRR): 1.82; 95% CI:

1.22-2.71), as was homelessness (RRR: 3.02; 95% CI: 2.02-4.50), being stopped or arrested by police (RRR: 1.77; 95% CI: 1.18-2.64), and having been enrolled in a drug/alcohol rehabilitation center in the last six months (RRR: 4.13; 95% CI: 2.25-7.04).

In terms of substances used, PWID who reported recent use of fentanyl (RRR: 3.73; 95% CI: 2.48-5.72) or china white (RRR: 2.23; 95% CI: 1.51-3.51) had significantly greater risk of overdose. Having used heroin (RRR: 2.30; 95% CI: 1.26-4.72), oxycontin (RRR: 2.05; 95% CI:1.03-3.66), cocaine (RRR: 2.23; 95% CI: 1.36-3.49), speedballs (RRR: 2.98; 95% CI: 1.68-4.96), methamphetamine (RRR: 2.85; 95% CI: 1.56-5.85), or PCP/Angel dust (RRR: 3.46; 95% CI: 1.79-6.08) was also associated with past six-month overdose. Importantly, drug categories were not mutually exclusive and most participants reported using multiple substances in the past six months. Those who reported polysubstance injection were at greater risk of overdose as well (RRR: 4.62; 95% CI: 2.71-8.49). There was a significant association between overdose risk and using china white but not believing it was fentanyl (RRR: 2.39; 95% CI: 1.52-3.67). Counter to our hypothesis, we did not find cross-border drug use to be associated with recent overdose.

1.3.5 Multivariate analyses

Table 3 provides two multivariate models examining our hypotheses that use of china white is associated with an increased risk of overdose, and that participants who use china white but do not believe it contains fentanyl have a higher overdose risk. Model 1 demonstrates the relative risk of using china white and fentanyl. Model 2 includes a dummy variable with three levels where the reference group is those who did not use china white in the past six months, relative to those who used china white and did not believe it contained fentanyl, and those who used china white and did believe it contained fentanyl. In Model 1, after adjusting for sex and race, a significant interaction between intentional fentanyl use and china white use was observed (p=0.02) indicating that use of fentanyl moderates the association between china white use and overdose. More specifically, for PWID who did not report using fentanyl, use of china white was associated with a greater risk of overdose relative to PWID who intentionally use fentanyl (Figure 2 in supplement). Other factors independently associated with elevated overdose risk were having been enrolled in a drug/alcohol rehabilitation center (Adjusted Risk Rate Ratio (AdjRRR): 2.33; 95% CI: 1.40-3.86), having been recently stopped or arrested by police (AdjRRR: 1.56; 95% CI: 1.10-2.22), and experiencing homelessness (AdjRRR: 1.95; 95% CI: 1.34-2.84). Neither controlling for city of residence nor removing race and sex from the model significantly altered parameter estimates. The final model was also unchanged when including the injection frequency variable. Of note, although polysubstance injection was a significant predictor of overdose in a univariate model, we ultimately excluded it from the multivariate models due to its high correlation with both reported fentanyl and china white use.

To further examine the influence of unknowingly using fentanyl on overdose risk, in Model 2 we replaced the “china white use” variable with a composite variable combining use of china white with participant beliefs about whether it contained fentanyl. Model 2 shows that relative to participants who did not use china white, those

who used china white and did *not* believe it was fentanyl had a significant increased risk of recent overdose (AdjRRR: 1.98; 95% CI: 1.36-2.88). The remaining variables found to be significant in Model 1 remained significant in Model 2.

1.3.6 Relationship between using china white and believing it contains fentanyl

In our exploratory analysis, after controlling for sex and race, participants who identified fentanyl as a content of china white were 63% less likely to use china white in the last six months (Adjusted Odds Ratio: 0.37; 95% CI: 0.20-0.66) (Table 4).

1.4 Discussion

In this study of PWID in the US-Mexico border region, we found that nearly 16% of participants experienced a nonfatal overdose within the six months prior to baseline interviews, and that knowingly using fentanyl and unknowingly using fentanyl via china white were both independently associated with a higher overdose risk as was homelessness, police interactions, and enrollment in a drug/alcohol rehabilitation center. Although the relationship between fentanyl and overdose risk is well established, the fact that both intentional and unintentional fentanyl use were significantly associated with overdose risk has important implications for prevention.

Despite reports in the region that powder heroin like china white often contains fentanyl (Fleiz et al., 2020), most PWID who recently used china white did not think it contained fentanyl, yet using china white significantly increased overdose risk. These results indicate an urgent need to inform PWUD in the San Diego/Tijuana area of the risk of overdose associated with china white use, and that it may often contain fentanyl. Our findings also underscore the need to develop real-time drug surveillance and public health alert systems to caution PWUD about overdose risks associated with the local drug supply. Such systems have operated in European countries since the 1990s to help PWUD avoid unintentionally ingesting dangerous adulterants (Brunt et al., 2017), and have more recently been implemented in Canada (Buxton et al., 2019). In the U.S., most drug surveillance programs are operated by the Drug Enforcement Agency or Central Intelligence Agency, and others such as the National Drug Early Warning System cannot always share real-time data publicly.

Community drug checking programs offer a method for identifying trends in the local drug supply and allow PWUD to determine the contents of their drugs before using them. Many PWUD report safer drug use behaviors in response to a positive fentanyl result following drug checking with fentanyl test strips, including using smaller amounts, using more slowly, using in the presence of others, doing a tester shot, keeping naloxone nearby, or discarding the drug altogether (Allen et al., 2020; Goodman-Meza et al., 2022; Krieger et al., 2018; Peiper et al., 2019). Notably, these safer behaviors are not always feasible; for example, while naloxone has been extensively distributed through government, healthcare, and community harm reduction efforts in San Diego, the overdose antidote is considered a psychoactive substance and is thus highly regulated and not widely accessible in Mexico (Chaparro, 2022). Despite positive anticipated behavior change, fentanyl test strips, the most widespread drug checking

technology in the U.S., have limited utility in that they only indicate if fentanyl is present, but cannot determine fentanyl concentration in a given drug sample (Green et al., 2020). Community drug checking programs utilizing advanced technologies such as Fourier transform infrared (FTIR) or hand-held Raman spectrometers allow for the quantification of multiple substances in a given drug sample, including fentanyl and its analogs, benzodiazepines, or cutting agents (Carroll et al., 2022). As of baseline data collection for this study, advanced drug checking services were not available for the San Diego nor Tijuana drug user community. Having additional knowledge of the contents and concentrations of specific substances in their drugs, particularly fentanyl, may help PWUD modify drug use behaviors to prevent overdose. There are reports of other dangerous contaminants in the illicit opioid supply in North America, including novel psychoactive benzodiazepines (Laing et al., 2021) and xylazine, a veterinary tranquilizer (Friedman et al., 2022c), that are also detectable with advanced drug checking technologies. However, given use of these advanced technologies in a community drug checking context is relatively new, there is a need to understand how PWUD respond to varying concentrations of fentanyl or other adulterants in their drugs, evaluate barriers to program uptake, and estimate the efficacy of various types of drug checking programs in reducing the incidence of overdose in diverse settings. Additionally, because some PWUD may prefer fentanyl, it is important to develop harm reduction strategies to accompany advanced drug checking information.

Our findings also reinforce previous studies that found other structural factors to be associated with overdose risk. PWUD are at greater risk of overdose following a period of detoxification while in rehabilitation, drug treatment, or jail/prison as their drug tolerance has decreased but cravings and triggers may persist (Binswanger et al., 2007; Sordo et al., 2017; Wines et al., 2007). Of particular concern, involuntary drug treatment programs in Mexico that are still in operation significantly increase non-fatal overdose risk among PWID (Rafful et al., 2018). Expanding access and reducing barriers to engagement and retention in programs that offer medications for opioid use disorder (MOUD) in combination with overdose prevention interventions could protect persons with an opioid addiction from relapse at a time in which they are particularly vulnerable to overdose (Ray et al., 2022; Volkow and Wargo, 2018; Wakeman et al., 2020).

Fear of police is associated with riskier substance use behaviors that increase the probability of overdose and infectious disease transmission, such as rushed injection or avoidance of harm reduction services (Baker et al., 2020; Cooper et al., 2005). Training police in harm reduction (Baker et al., 2021; Khorasheh et al., 2019) and decriminalizing drug use (Blumenauer et al., 2022; Bonn et al., 2020) may mitigate the negative impact of police interactions on overdose risk. Police trainings have shown promising results in terms of police support for and knowledge of harm reduction efforts such as syringe exchange and naloxone distribution programs (Davis and Beletsky, 2009; Ray et al., 2015). Despite these efforts, police still operate in a context that often prioritizes criminalization over the health and well-being of PWUD (Beletsky et al., 2013; Morales et al., 2018). Decriminalization of drug use alone is also insufficient; Mexico's decriminalization of drug possession in 2009 did not positively impact the risk environment for PWID in Tijuana, partially due to a lack of police training on new policies (Beletsky et al., 2016). A subsequent training for police in Tijuana led to an

increase in knowledge related to decriminalization laws, highlighting the need for legal training for police to accompany policy reforms (Arredondo et al., 2017). Although trainings may impact officers' intentions in their interactions with PWUD, it is not clear that this would lead to substantial reforms in policing practices, particularly given ethnographic reports from Tijuana documenting purposeful, extralegal police brutality toward PWUD and routinized corruption (Calderón-Villarreal et al., 2022; Friedman et al., 2022b; Martinez et al., 2007).

Given the negative consequences of the policing and criminalization of PWUD, harsher legal penalties for fentanyl possession are not an appropriate solution for addressing public health issues related to the ubiquity of fentanyl in the illicit drug supply. Contrary to what some lawmakers have proposed (Law, 2022), enacting more severe penalties for fentanyl possession is unlikely to reduce possession or overdose rates, as our study shows that PWUD are often unaware that the substances they use contain fentanyl. Moreover, harsher penalties for drug possession have historically not resulted in decreased substance use or overdose, and have had disparate impacts on minorities (PEW, 2018; Tonry and Melewski, 2008). Furthermore, laws that specify "knowingly" possessing fentanyl, such as a recently proposed Colorado law (Cooke et al., 2022), may also disincentivize PWUD from using drug-checking services, as detection of fentanyl in their drug supply could implicate them in a felony.

Other studies consistently detect associations between homelessness and many negative health outcomes, including overdose (van Draanen et al., 2020; Wagner et al., 2015; Yamamoto et al., 2019). Housing shelters are typically underprepared to support PWUD experiencing homelessness and many shelters prohibit use of any substances (Wallace et al., 2018), leaving vulnerable PWUD without shelter. Housing First programs providing housing and services for people experiencing homelessness without a requirement of abstinence can decrease overdose risk (Doran et al., 2022), hospitalizations and emergency department visits, and improve rates of stable housing and quality of life (Aubry et al., 2015; Baxter et al., 2019). Other harm reduction interventions for housing unstable populations, such as supervised consumption facilities and MOUD, have also reduced overdose mortality and morbidity (Magwood et al., 2020). At the time of this study, there were no safe consumption services in either San Diego or Tijuana, although the first unsanctioned safe consumption site in Latin America was opened for women in nearby Mexicali in 2021 (Goodman-Meza et al., 2022).

We did not find cross-border drug use to be associated with recent overdose. It is possible that PWID in our study who travel to Mexico to use drugs are not particularly naïve to the Tijuana drug scene given some San Diego PWUD commonly travel to and use substances with residents in Tijuana (Bórquez et al., 2019). Alternatively, despite having used drugs in Mexico in the past, perhaps they do not frequently engage in cross-border drug use. Our study suggests that PWUD in both cities would benefit from learning the contents of their drug supply to decrease their risk of overdose.

1.4.1 Limitations

Due to the criminalized nature of drug use, random sampling was not possible for recruitment, limiting our study's generalizability. Furthermore, although drug markets are intertwined globally, the specific drug supply varies geographically, limiting the applicability of our study findings to other locations. Our cross-sectional study design does not permit inferences about temporality or causality. For example, some PWID who used china white may have begun to believe it contains fentanyl only after having overdosed. Relatedly, the measure created to capture use of china white in the context of participants' beliefs about its contents was a proxy measure for unknowingly using fentanyl; imprecision in this measure may have underestimated associations with the outcome. This study did not include confirmatory testing of PWID conjectures about the contents of china white and the extent to which it contains fentanyl, which may differ over time and by neighborhood. Finally, all survey items were self-report and thus may have been subject to recall or social desirability biases.

1.5 Conclusions

Our findings suggest that knowingly and unknowingly using fentanyl via china white were both independently associated with recent overdose, suggesting that drug checking services be implemented as overdose prevention strategies such that PWUD can determine the contents of the drugs they use and related public health alerts can inform the wider community about drug contents. Future research should determine how advanced drug checking services influence PWUD behavior. Additionally, this study emphasizes the relevance of structural factors including drug rehabilitation/treatment, policing practices, and homelessness in overdose prevalence, highlighting an urgent need for expanded harm reduction policies and practices to address overdose in the context of wholesale street drug markets shifting toward more toxic synthetic products.

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Table 1. Descriptive characteristics in a cohort of people who inject drugs in San Diego, California and Tijuana, Mexico, stratified by recent overdose, N=612

Baseline Characteristics	No past 6-month overdose N=515	Past 6-month overdose N=97	p-value	Total N=612
Country of Residence (U.S.) (n(%))	342 (66.4)	68 (70.1)	0.55	410 (67.0)
Age (mean (SD))	43.44 (10.7)	40.77 (11.0)	0.03	43.02 (10.8)
Sex (Male) (n(%))	377 (73.2)	76 (78.4)	0.35	453 (74.0)
Race (White) (n(%))	171 (33.2)	49 (50.5)	**0.002**	220 (35.9)
Hispanic ethnicity (n(%))	379 (73.6)	61 (62.9)	**0.04**	440 (71.9)
Married (n(%))	98 (19.0)	18 (18.6)	1.0	116 (19.0)
Homelessness (n(%))*	88 (17.1)	44 (45.4)	**<0.001**	132 (21.6)
Hours per day spent in the street (mean (SD))*	15.09 (7.46)	18.22 (7.18)	**<0.001**	15.58 (7.50)
Prior overdose (n(%))**	221 (42.9)	97 (100.0)	**<0.001**	318 (52.0)
Stop or arrest by police (n(%))*	147 (28.5)	43 (44.3)	**0.003**	190 (31.0)
Recent enrollment in a drug/alcohol rehabilitation center (n(%))*	10 (1.9)	14 (14.4)	**<0.001**	24 (3.9)
Cross-border drug use (n(%))*	177 (34.4)	29 (29.9)	0.46	206 (33.7)
Past 6-month substance use				
Average number of daily drug injections (mean (SD))*	2.27 (1.55)	2.79 (1.35)	**0.002**	2.36 (1.53)
Heroin (n(%))*	397 (77.1)	87 (89.7)	**0.008**	484 (79.1)
fentanyl (n(%))*	128 (24.9)	62 (63.9)	**<0.001**	190 (31.0)
Oxycontin (n(%))*	25 (4.9)	11 (11.3)	**0.024**	36 (5.9)
Other Rx opioids (n(%))*	14 (2.7)	7 (7.2)	0.05	21 (3.4)
China white (n(%))*	78 (15.1)	33 (34.0)	**<0.001**	111 (18.1)
Cocaine (n(%))*	52 (10.1)	23 (23.7)	**0.001**	75 (12.3)
Speedball (n(%))*	22 (4.3)	16 (16.5)	**<0.001**	38 (6.2)
Methamphetamine (n(%))*	374 (72.6)	87 (89.7)	**0.002**	461 (75.3)
PCP/Angel Dust (n(%))*	12 (2.3)	12 (12.4)	**<0.001**	24 (3.9)
Ecstasy (n(%))*	31 (6.0)	5 (5.2)	0.92	36 (5.9)
Ketamine (n(%))*	3 (0.6)	1 (1.0)	0.50	4 (0.7)

Hallucinogens (n(%))*	20 (3.9)	5 (5.2)	0.76	25 (4.1)
Inhalants (n(%))*	4 (0.8)	0 (0.0)	1.000	4 (0.7)
Tranquilizers (n(%))*	124 (24.1)	32 (33.0)	0.09	156 (25.5)
Barbiturates (n(%))*	1 (0.2)	2 (2.1)	0.07	3 (0.5)
Polysubstance injection (n(%))***	261 (50.7)	83 (85.6)	**<0.001**	344 (56.2)
China white use and content beliefs				
Used china white, did not believe was fentanyl*	66 (12.8)	29 (29.9)	**<0.001**	95 (15.5)
Used china white, believed was fentanyl*	12 (2.3)	4 (4.1)	**<0.001**	16 (2.6)

*each indicated variable refers to the 6 month period prior to baseline interview
**not including past 6-month overdose(s)
***polysubstance injection means any opioid injected simultaneously with a stimulant – other types of drug combinations (such as poly-opioid use) were not asked of participants

Figure 1. Participant beliefs about the contents of china white among people who inject drugs in San Diego, California and Tijuana, Mexico, n=612*

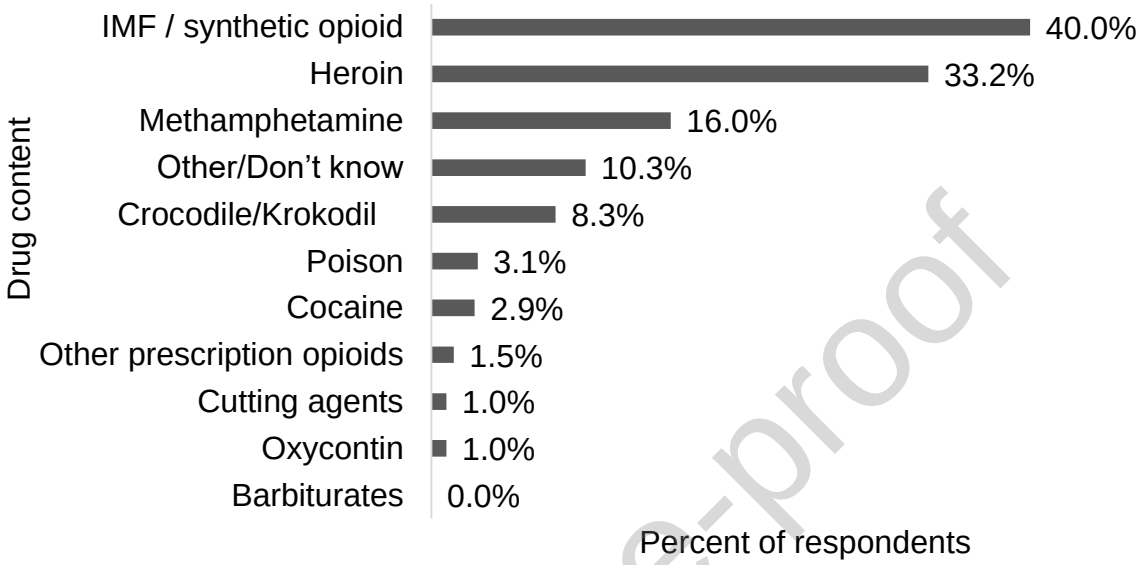

Table 2. Univariate associations with recent overdose in a cohort of people who inject drugs in San Diego, California and Tijuana, Mexico, N=612		
Baseline characteristics	RRR	95% CI
Country of Residence (U.S.) (n(%))	1.16	0.76, 1.81
Age (mean (SD))	0.98	0.96, 1.00
Sex (Male) (n(%))	1.27	0.80, 2.11
Race (White) (n(%))	1.82	1.22, 2.71
Hispanic ethnicity (n(%))	0.66	0.44, 1.01
Married (n(%))	0.97	0.57, 1.59
Homelessness (n(%))*	3.02	2.02, 4.50
Hours per day spent in the street (mean (SD))*	1.05	1.02, 1.08
Stop or arrest by police (n(%))*	1.77	1.18, 2.64
Recent enrollment in a drug/alcohol rehabilitation center (n(%))*	4.13	2.25, 7.04
Cross-border drug use (n(%))*	0.84	0.54, 1.28
Past 6-month substance use		
Average number of daily drug injections*	1.22	1.06, 1.41
Heroin (n(%))*	2.30	1.26, 4.72
fentanyl (n(%))*	3.73	2.48, 5.72
Oxycontin (n(%))*	2.05	1.03, 3.66
China white (n(%))*	2.23	1.51, 3.51
Cocaine (n(%))*	2.23	1.36, 3.49
Speedball (n(%))*	2.98	1.68, 4.96
Methamphetamine (n(%))*	2.85	1.56, 5.85
PCP/Angel Dust (n(%))*	3.46	1.79, 6.08
Ecstasy (n(%))*	0.87	0.31, 1.93
Hallucinogens (n(%))*	1.28	0.45, 2.83
Tranquilizers (n(%))*	1.44	0.93, 2.18
Polysubstance injection (n(%))***	4.62	2.71, 8.49
China white use and content beliefs		
Did not use china white (reference group)*	-	-
Used china white, did not believe was fentanyl*	2.39	1.52, 3.67
Used china white, believed was fentanyl*	1.96	0.59, 4.74
*each indicated variable refers to the 6 month period prior to baseline interview		

Table 3. Multivariate Poisson regression models of correlates independently associated with past 6-month overdose in a cohort of people who inject drugs in San Diego, California and Tijuana, Mexico, N=612

Model 1 with china white use only				Model 2 with china white use and content beliefs			
	Adj RRR	95% CI	p-value		Adj RRR	95% CI	p-value
Fentanyl use*	3.63	2.12, 6.22	**<0.001**	Fentanyl use*	2.66	1.74, 4.06	**<0.001**
China white use*	3.54	1.91, 6.55	**<0.001**	Did not use china white (reference group)*	**-**	**-**	**-**
				Used china white, did *not* believe it was fentanyl*	1.98	1.36, 2.88	**0.000**
				Used china white, believed it was fentanyl*	1.93	0.83, 4.45	0.13
Recent enrollment in a drug/alcohol rehabilitation center *	2.33	1.40, 3.86	**0.001**	Recent enrollment in a drug/alcohol rehabilitation center *	2.24	1.32, 3.81	**0.003**
Stop or arrest by police*	1.56	1.10, 2.22	**0.01**	Stop or arrest by	1.62	1.15,	**0.006**

				police*		2.28	
Homelessness*	1.95	1.34, 2.84	**0.001**	Homelessness*	1.98	1.35, 2.91	**0.001**
Race (White vs. Other)	1.32	0.91, 1.91	0.15	Race (White vs. Not White)	0.86	0.72, 1.03	0.11
Sex (Male vs. Female)	1.17	0.77, 1.79	0.47	Sex (Male vs. Female)	1.17	0.77, 1.79	0.46
China white use*fentanyl use	0.40	0.19, 0.85	**0.02**				
Interaction: Simple main effects							
Effect of china white use (yes vs. no) in people who reported fentanyl use	1.43	0.95, 2.15	**0.09**				
Effect of china white use (yes vs. no) in people who reported *no* fentanyl use	3.54	1.91, 6.55	**<0.001**				
Effect of fentanyl use (yes vs. no) in people who reported china white use	1.46	0.82, 2.60	0.195				
Effect of fentanyl use (yes vs. no) in people who reported *no* china white use	3.63	2.12, 6.22	**<0.001**				
*each indicated variable refers to the 6-month period prior to baseline interview							

Table 4. Logistic regression model of association between recent use of china white* and belief that china white contains fentanyl in a cohort of people who inject drugs in San Diego, California and Tijuana, Mexico, N=612

	AdjOR	95% CI	p-value
Believing china white contains fentanyl	0.23	0.13, 0.39	**<0.001**
Race (White vs. Not White)	0.73	0.41, 1.24	0.365
Sex (Male vs. Female)	0.99	0.57, 1.81	0.931
*refers to the 6-month period prior to baseline interview			

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Conflict of Interest
No conflict declared.

Contributors
SAS, AHV, and MGR made substantial contributions to study conception and design. CFV lead data acquisition. SAS, KB, DA, TLP, JF, and PB contributed to the analysis and interpretation of data and drafting the manuscript. All authors reviewed and contributed edits to the manuscript.

Highlights

- Fentanyl is commonly found in heroin and other illicit drugs in North America
- Overdose was associated with use of powder heroin known as *china white*
- Most who used china white did not believe it contained fentanyl
- Those who believed china white contained fentanyl were less likely to use it
- Harm reduction measures like drug checking may help people avoid overdose