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Risk of non-fatal overdose and polysubstance use in a longitudinal study with people who inject drugs in Tijuana, Mexico

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Abstract

Introduction. *Among people who inject drugs (PWID), polysubstance use has been associated with fatal and non-fatal overdose (NFOD). However, the risk of overdose due to the cumulative number of various recently used drug types remains unexplored. We estimated the risk of NFOD for different polysubstance use categories among PWID in Tijuana, Mexico.* ***Methods.*** *Data came from 661 participants followed for 2 years in Proyecto El Cuete-IV, an ongoing prospective cohort of PWID. A multivariable Cox model was used to assess the cumulative impact of polysubstance use on the time to NFOD. We used the Cochran-Armitage test to evaluate a dose–response relationship between number of polysubstance use categories and NFOD.* ***Results.*** *We observed 115 NFOD among 1029.2 person-years of follow-up (incidence rate: 11.2 per 100 person-years; 95% confidence interval [CI] 9.3-13.3). Relative to those who used one drug class, the adjusted hazard ratio of NFOD for individuals reporting using two drug classes was 1.11 (95% CI 0.69-1.79), three drug classes was 2.00 (95% CI 1.16-3.44) and for those reporting three compared to two was 1.79 (95% CI 1.09-2.97). A significant Cochran-Armitage trend test (*$P < 0.001$*) suggested a dose–response relationship.* ***Discussion and Conclusions.*** *Polysubstance use was associated with increased risk of NFOD with a dose–response relationship over 2 years. We identified a subgroup of PWID at high risk of NFOD who reported concurrent use of opioids, stimulants and benzodiazepines. Prioritising tailored harm reduction and overdose prevention interventions for PWID who use multiple substances in Tijuana is needed.* [Rivera Saldana CD, Abramovitz D, Meacham MC, Gonzalez-Zuniga P, Rafful C, Rangel G, Strathdee SA, Cepeda J. Risk of non-fatal overdose and polysubstance use in a longitudinal study with people who inject drugs in Tijuana, Mexico. *Drug Alcohol Rev* 2021]

Key words: polysubstance use, drug overdose, injected drug use.

Introduction

Overdose has been identified as a major cause of death among people who inject drugs (PWID) [1,2]. The risk of a fatal overdose increases the first year after a non-fatal overdose (NFOD) [1,3]. Among PWID, injecting frequency (daily or more) and homelessness have been associated with NFOD [3]. The role of specific substances, such as heroin, cocaine, benzodiazepine and methamphetamine, on both NFOD and fatal overdose has been studied among PWID in a range of global settings, including Canada [4–6], the United Kingdom [7] and the United Sates [8–11]. In general, these studies point to an increased risk of fatal or NFOD associated with polysubstance use. Other studies have used latent class analysis to examine differences in recent overdose rates between classes characterised by drug and route of administration, finding that individuals in multidrug

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and multi-route classes had the highest prevalence of recent overdose [11,12]. However, the number and type of drugs used potentially leading to an NFOD episode are rarely quantified [13]. Furthermore, most of the previous work has been done in high-income settings and may not be generalisable to low- and middle-income countries characterised by poor access to health services and resources [12].

Situated along a major drug corridor to the United States, Tijuana is the city with the highest prevalence of illegal substance use in Mexico [14]. In 2016, the state of Baja California (BC), where Tijuana is located, had a prevalence of illegal drug use of 7.6% among adults (nationwide 4.6%) and the highest prevalence of amphetamine use in the country of 5% (nationwide 1.5%) [15]. Data from one of Mexico's largest drug treatment programs showed that BC had the second highest prevalence of heroin use among treatment seekers in the country (12.6%), second only after the state of Chihuahua (16%) [16]. From previous work among a sample of polysubstance using PWID in Tijuana, heroin injection was the primary drug and route of choice (95%), including 50% of the sample co-injecting heroin and methamphetamine and an additional 15% co-injecting heroin and cocaine [12]. Participants also reported injecting methamphetamine (28%) and cocaine (8%) alone. Benzodiazepine ingestion was also common (20%) [12]. In this same sample, a different study found benzodiazepine use independently associated with NFOD (adjusted odds ratio 11.92, 95% confidence interval [CI] 1.41-2.61) [17], but it was unclear if it was used concurrently with other drug classes and how it may affect risk of NFOD.

The objective of this analysis was: (i) to characterise the polysubstance use profiles among PWID in Tijuana, Mexico, through identifying the type and number of different drugs used concurrently; and (ii) to assess the cumulative impact of polysubstance use on the time to NFOD over 2 years. We hypothesised that individuals who reported a greater number of substances would have significantly increased risk of NFOD compared to individuals who use fewer drug types.

Methods

Study procedures

We used data from an ongoing prospective cohort of PWID in Tijuana, Mexico (*El Cuete-IV*). Between 2011 and 2013, baseline data were collected for 734 participants with follow-up surveys every 6 months [18]. As detailed elsewhere [18], targeted sampling consisting of street outreach in 10 neighbourhoods across Tijuana was used to recruit participants who were 18 years of age or older, had injected drugs in the past month and were currently living in Tijuana. At baseline and biannually thereafter, trained interviewers using computer-assisted participant interview technology administered questionnaires to collect data on socio-demographics, drug-use behaviours, drug treatment experiences, criminal justice involvement, migration history and self-reported drug-related harms and health outcomes. Participant retention was achieved through different follow-up strategies that were executed by a binational (Mexico and United Sates) outreach team. For example, during recruitment, staff members collected locator data to facilitate participant follow-up (e.g. visiting their residences or socialising locations). Between study follow-ups, the outreach team repeatedly contacted participants by telephone check-ins or street-based tracking [18]. Participants were given a USD $20 stipend at each study visit for their time and transportation [2]. This study was approved by the Ethics Board at the University of California San Diego and Xochicalco University in Tijuana. All participants provided written informed consent.

Exposure

Our exposure of interest was cumulative polysubstance use in the past 6 months assessed at baseline. To construct this variable, we first identified the main drugs used by PWID in our sample, and then grouped them into classes. Based on previous work [12], main drugs were chosen as those with at least 5% prevalence. We excluded marijuana from our definition of polysubstance use as it was used in combination with other drugs in only a negligible number of NFOD (3/117) outcomes [17]. The drug classes were specified as: (i) opioids (which in our sampled comprised only heroin); (ii) stimulants (in our sample included methamphetamine and cocaine); and (iii) benzodiazepines (examples to participants in the survey included Diazepam [Valium], Ativan [Lorazepam] and Restoril [Temazepam]). Polysubstance use was assessed through reported consumption of more than one of these drug classes administered through any route or frequency in the past 6 months. Our exposure variable consisted of three categories: participants who reported using only one drug class; participants who reported using two drug classes; and participants who reported consumption of all three drug classes.

Outcome

The outcome was the time to the first self-reported NFOD after baseline over a 2-year follow-up period. We used the following measure to define NFOD: '*In the last 6 months, how many times have you overdosed?*

This includes any situation where you passed out and couldn't wake up or your lips turned blue'. This overdose description read to participants during the survey corresponds to an opioid overdose. In each follow-up survey, participants were asked if they experienced an overdose during the past 6 months. For those who

Table 1. *Baseline characteristics of people who inject drugs enrolled in the El Cuete-IV cohort in Tijuana Mexico, stratified by observed non-fatal overdose over a 2-year follow-up*

Variable	Overall	No overdose	Non-fatal overdose	*P*-value[a]
Total, *n* (%)[b,c]	**661**	546 (82.6)	115 (17.4)	
Sociodemographics				
Age, median [IQR]	37.0 [31.0, 44.0]	38.0 [32.0, 45.0]	33.0 [29.0, 41.0]	<0.001
Gender				
Male	405 (61.3)	341 (62.5)	64 (55.7)	0.209
Female	256 (38.7)	205 (37.5)	51 (44.3)	
Education years, median [IQR]	8.0 [6.0, 10.0]	8.0 [6.0, 10.0]	8.0 [6.0, 9.75]	0.755
Income from formal job				
No	572 (86.5)	472 (86.4)	100 (87.0)	1
Yes	89 (13.5)	74 (13.6)	15 (13.0)	
Hours daily spent in street, median [IQR]	12.0 [8.0, 19.0]	12.0 [8.0, 18.0]	12.0 [9.5, 20.0]	0.144
Recently incarcerated (past 6 months)				
No	404 (61.1)	339 (62.1)	65 (56.5)	0.314
Yes	257 (38.9)	207 (37.9)	50 (43.5)	
Drug use related				
Polysubstance use (drug classes)				
One	263 (39.8)	228 (41.8)	35 (30.4)	<0.001
Two	300 (45.4)	251 (46.0)	49 (42.6)	
Three	98 (14.8)	67 (12.3)	31 (27.0)	
Years since first injection, median [IQR]	16.0 [9.0, 22.0]	16.0 [10.0, 23.0]	14.0 [7.0, 20.0]	0.062
Heroin injecting frequency				
Daily	594 (91.0)	488 (90.5)	106 (93.0)	0.517
Less than daily	59 (9.0)	51 (9.5)	8 (7.0)	
Ever sought help from hit doctor				
No	260 (61.9)	223 (65.0)	37 (48.1)	0.008
Yes	160 (38.1)	120 (35.0)	41 (52.6)	
Getting professional help for drugs/alcohol				
No	284 (43.0)	246 (45.1)	38 (33.0)	0.024
Yes	377 (57.0)	300 (54.9)	77 (67.0)	
Recent release from rehab/treatment				
No	602 (91.1)	509 (93.2)	93 (80.9)	<0.001
Yes	59 (8.9)	37 (6.8)	22 (19.1)	
History of overdose				
Ever	363 (54.9)	276 (50.5)	87 (75.7)	<0.001
Never	298 (45.1)	270 (49.5)	28 (24.3)	
Alcohol use				
None	402 (71.8)	344 (74.5)	58 (59.2)	0.009
Moderate	82 (14.6)	62 (13.4)	20 (20.4)	
High	76 (13.6)	56 (12.1)	20 (20.4)	
Cross-border mobility related				
Ever deported from the United States				
No	510 (77.2)	419 (76.7)	91 (79.1)	0.665
Yes	151 (22.8)	127 (23.3)	24 (20.9)	
Injected while in the United States				
No	420 (63.5)	340 (62.3)	80 (69.6)	0.171
Yes	241 (36.5)	206 (37.7)	35 (30.4)	

[a]*P*-value for groupwise comparison test: χ^2-test for categorical variables and Kruskal-Wallis rank sum test otherwise. [b]Not all variables add up to 661 due to missing values. Four variables had missing values within the range of 0.2–2.4% of the total sample. Receiving help from hit doctor has 36.5% missing responses due to being added later to the survey. Alcohol use has 15.3% missing observations due to not being assessed until the first visit after baseline, which was answered by a smaller number of participants. [c]All behaviours are measured in past 6 months. IQR, interquartile range.

had, we calculated the time the event occurred as the mid-point between the date of the visit in which the event was reported and the date of the previous visit. Individuals who did not experience the event during the study period were right censored. We chose a 2-year follow-up period in order to observe a relatively frequent event like NFOD that could be reasonably attributed to baseline characteristics and before substantial study attrition occurred.

Potential confounders

We selected potential confounders *a priori* based on factors associated with overdose in previous studies among PWID [1,6,8,17,19], including characteristics relevant to the sample of PWID in Tijuana [17,20]. The drug-related variables included: years since first injection, heroin injecting frequency (daily vs. not-daily, past 6 months), ever seeking help from a hit doctor (person who helps with injecting drugs), recently released from rehab/treatment (past 6 months, constructed from the survey question, 'When did you enter [this] rehab/drug treatment center the last time?'), ever getting professional help for drugs/alcohol and having ever overdosed at baseline. We also included a variable for alcohol use with three categories (none, moderate and high), constructed from two different questions inquiring about frequency and number of alcoholic drinks usually consumed. Importantly, these two alcohol-use questions were not assessed in the baseline questionnaire and appeared in the first follow-up survey after baseline. We assumed that alcohol-use patterns did not change substantially from baseline to the first follow-up visit. The sociodemographic variables included: age, gender, years of education, income from a formal source, recent incarceration (past 6 months) and hours spent daily in the street as a proxy for homelessness. We also considered variables related to Tijuana's border region, such as having ever been deported from the United States and ever injecting drugs while in the United States. All potential confounders were assessed at baseline.

Analytic sample

Of the total 734 participants, 73 (10%) were excluded from the analysis (63 were lost to follow-up, i.e. had zero follow-up visits, and 11 had missing values for the main predictor). Excluded participants did not differ significantly from included participants on baseline socio-demographic, drug use or Tijuana border region characteristics, but daily heroin injection at baseline was significantly higher for included participants (91% vs. 81%, $P = 0.02$). The final analytic sample comprised of 661 participants.

Statistical analysis

We compared baseline characteristics between those who experienced NFOD during the 2-year follow-up and those who did not. For categorical variables, we reported frequencies and proportions and for continuous variables medians and interquartile ranges. Individuals who experienced an NFOD were compared to those who did not experience a NFOD by conducting a Kruskal-Wallis test for comparisons with respect to continuous variables and a χ^2-test for comparisons with respect to categorical variables. We estimated the incidence rate of NFOD during the 2-year follow-up by dividing the number of NFOD cases by the total person-years at risk.

To investigate the association between poly-substance use and the risk of NFOD, we conducted a Cox proportional hazards model (Cox PH model) with the time to NFOD as the outcome. Kaplan–Meier curves were plotted to depict the survival function of NFOD by each polysubstance use category. We assessed the underlying assumptions for the Cox PH model, that is verifying the proportional hazards assumption was met over the 2-year follow-up, through plotting log–log curves and Schoenfeld residuals [21]. Meeting this assumption suggests no need to time-update our covariates during the follow-up period [22]. Then, a univariable Cox PH model was used to obtain unadjusted hazard ratios and 95% CIs for those who reported consuming two and three drug

Table 2. *Description of polysubstance use categories by drug types from analytical sample (*n = *661)*

Polysubstance category	Category total	Main drug type(s) used by category, *n* (%)		
		Opioids	*Stimulants*	*Benzodiazepines*
One drug type	263	246 (93.5)	14 (5.3)	3 (1.1)
		Opioids and stimulants	*Opioids and benzodiazepines*	*Stimulants and benzodiazepines*
Two drug types	300	271 (90.3)	25 (8.3)	4 (1.3)
			Opioids and stimulants and benzodiazepines	
Three drug types	98		98 (100)	

classes with respect to those reporting consuming only one (i.e. single substance use class), as well as for those reporting consuming three drug classes compared to two. Next, multiple univariable Cox PH models were used to test the association between the potential confounders listed above and the outcome. Covariates with *P*-values <0.10 in univariable analyses were selected for inclusion in the multivariable model. Before the final multivariable model was determined, we assessed multicollinearity using variance inflation factors, but this was not detected. Finally, we tested for a dose–response relationship between polysubstance use categories and NFOD using the Cochran-Armitage trend test. This test

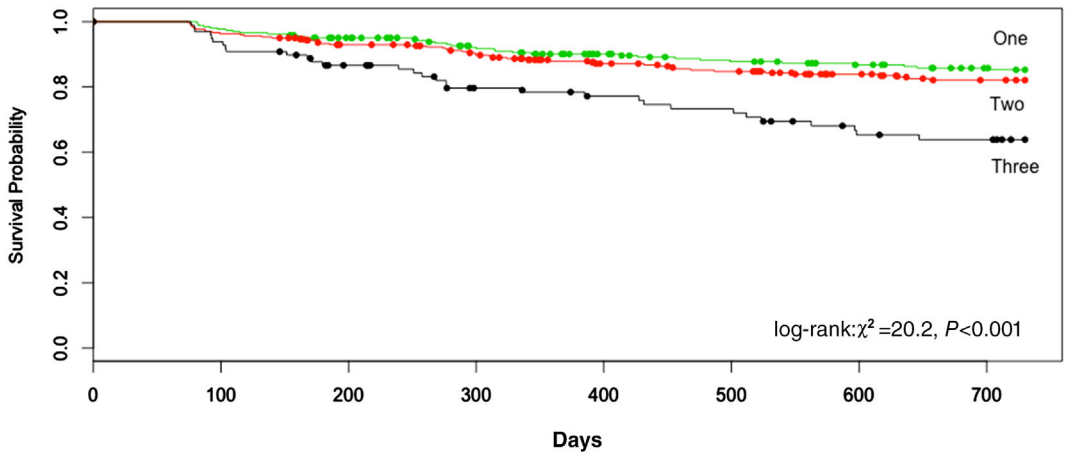

Figure 1. *Kaplan–Meier curves for time to non-fatal overdose by polysubstance use categories, 2-year follow-up.*

Table 3. *Unadjusted and adjusted Cox regression analyses for 2-year non-fatal overdose by polysubstance use categories and covariates (n = 661)*

	Unadjusted hazard ratios (HR)			Adjusted hazard ratios (aHR)[a]		
	HR	95% CI	*P*-value	aHR	95% CI	*P*-value
Age[b]	0.95	0.93, 0.98	**<0.001**	0.96	0.94, 0.99	**0.003**
Gender (*female [ref] vs. male*)	0.79	0.55, 1.14	0.21	—	—	—
Education years	1	0.94, 1.10	0.93	—	—	—
Income from formal job (*no [ref] vs. yes*)	0.99	0.57, 1.7	0.96	—	—	—
Hours daily spent in street	1.02	0.99, 1.05	0.19	—	—	—
Polysubstance use						
One versus two	1.25	0.81, 1.93	0.32	1.11	0.69, 1.79	0.66
One versus three	2.77	1.71, 4.50	**<0.001**	2.00	1.16, 3.44	**0.012**
Two versus three	2.23	1.42, 3.48	**<0.001**	1.79	1.09, 2.97	**0.022**
Years since first injection	0.98	0.96, 1.00	0.07	—	—	—
Frequency injecting heroin (*daily [ref] vs. not daily*)	0.8	0.39, 1.64	0.53	—	—	—
Getting professional help for drugs/alcohol (*no [ref] vs. yes*)	1.65	1.12, 2.44	**0.01**	1.15	0.73, 1.81	0.55
Recent release from rehab/treatment	2.75	1.73, 4.37	**<0.001**	2.23	1.29, 3.86	**0.004**
History of overdose at baseline (*never [ref] vs. ever*)	2.88	1.88, 4.41	**<0.001**	2.67	1.65, 4.31	**<0.001**
Alcohol use	1.85	1.11, 3.08	**0.018**	1.57	0.94, 2.62	0.09
None versus moderate						
None versus high	2.04	1.23, 3.40	**0.006**	1.78	1.06, 2.98	**0.028**
Ever deported from the United States (*yes [ref] vs. no*)	1.11	0.71, 1.75	0.64	—	—	—
Injected while in the United States (*no [ref] vs. yes*)	0.76	0.51, 1.13	0.18	—	—	—

[a]Multivariable adjusted Cox proportional hazard model. The final model included age, reported overdose at baseline, and receiving professional help for drug/alcohol. Years since first injection was removed due to high correlation with age (0.75). [b]Age was included as a continuous variable in single-year increments. CI, confidence interval.

examines the existence of a monotonic trend between an ordered categorical exposure and a dichotomous outcome [23].

Results

From 661 participants included in the analysis, 17.4% ($n = 115$) reported NFOD during the 2-year follow-up. In the overall sample, two-thirds (61%, $n = 405$) were male, the median age was 37 years (interquartile range: 31.0, 44.0), and the median number of years since first injection was 16 (interquartile range: 9.0, 22.0). Also, 594 (91%) individuals reported injecting heroin daily in the past 6 months and 363 (55%) reported ever having experienced an overdose. Among the study sample, 263 (40%) individuals reported using only one drug class in the past 6 months, 300 (45%) reported using any two drug classes and 98 (14.8%) reported using all three classes (Table 1). Among those in the one drug class category, 246 (93.5%) used opioids. In the two drug classes category, 271 (90.3%) used opioids and stimulants and 25 (8.3%) used benzodiazepines and opioids. Finally, 98 individuals (14.8% of the sample) were identified in the three drug classes category, reporting use of benzodiazepines, opioids and stimulants over the past 6 months. Table 2 offers a detailed description of each polydrug-use category by type of drug used and frequency.

During the 2-year follow-up period, we observed 115 NFOD over a total of 1029.2 person-years of follow-up, which resulted in an incidence rate of 11.2 per 100 person-years (95% CI 9.3-13.3). The log-rank test for the Kaplan–Meier curves indicated a significant difference in the probability of a NFOD between the three categories over the follow-up period ($P < 0.001$; Figure 1). Based on the univariable proportional hazards models, the unadjusted hazard ratio of NFOD for those using two drug classes compared to one was 1.25 (95% CI 0.81-1.93), for those using three drug classes compared to one was 2.77 (95% CI 1.71-4.50; Table 3) and for those using three drug classes compared to two was 2.23 (95% CI 1.42-3.48).

In multivariable analyses, the adjusted hazards ratio of NFOD for those using two drug classes compared to one was 1.11 (95% CI 0.69-1.79), for those using three drug classes compared to one was 2.00 (95% CI 1.16-3.44; Table 3) and for those using three drug classes compared to two was 1.79 (95% CI 1.09-2.97). Moreover, the Cochran-Armitage test was significant ($P < 0.001$), indicating a potential dose–response relationship between increasing number of drug class and elevated NFOD risk.

Discussion

Using data collected from 661 PWID in Tijuana, Mexico, we identified the type and number of different drugs concurrently used by study participants over the past 6 months. We found that polysubstance use, which in this population comprised mainly of opioids, stimulants and benzodiazepines, significantly increased the risk of experiencing NFOD. Opioids and benzodiazepines are both respiratory depressants, while stimulants increase heart rate and thus oxygen intake demands. Findings showed a twofold increase in the risk of NFOD for individuals who reported consuming all three drug types compared to those consuming one or two. However, the effect was not significant for individuals who reported consuming two drug types compared to those who used a single substance class. Moreover, findings indicate a dose–response association between an increasing number of drug types and the risk of NFOD.

Our results have important implications for overdose prevention. Approximately 15% of our sample corresponded to a high-risk subgroup of polysubstance-using PWID who used opioids, stimulants and benzodiazepines. Importantly, we identified the type and number of drug classes used by those individuals with the highest risk of NFOD in our sample. For example, our results highlight that the increased risk of NFOD associated with benzodiazepine use in previous work on this same population (adjusted odds ratio 1.92, 95% CI 1.41-2.61) [17], occurred alongside stimulants and opioids. This suggests that, in addition to the use of opioids and stimulants in this population, the use of benzodiazepines also contributes significantly to overdose risk. Some implications of our findings for PWID in Tijuana include the creation of safe consumption facilities and consolidating PWID's access to naloxone to reverse overdoses [24]. Additionally, since individuals at higher risk of a NFOD are also at a higher risk of overdose-related mortality, findings suggest that mortality prevention efforts should target those who use multiple classes of substances.

A recent study using the same PWID sample found that 25% of participants had died due to drug-related overdose [2]. In previous work in international settings, NFOD has been identified as a risk factor for subsequent fatal overdose [1]. Moreover, opioid overdose [25], benzodiazepine use and cocaine injection [26] have been independently associated to increased mortality among PWID. In our study, we have found how a number of these substances used concurrently over the same period increased risks of NFOD, potentially influencing increased mortality.

In our population of polysubstance using PWID in Tijuana, most used heroin daily (>90%), reinforcing previous work on the need for overdose prevention

interventions targeted at persons who use opioids through expanding access (e.g. affordability and proximity) to opioid agonist therapy and naloxone [27]. While some existing programs and organisations provide opioid agonist therapy in Tijuana, evidence points to widespread, structural barriers and high cost in drug treatment and prevention across the city [28,29]. Similarly, naloxone provision is not widespread and usually undersupplied in hospitals or other medical care units in Tijuana and across Mexico [30,31]. Moreover, the cost of naloxone might be prohibitive for most PWID in Tijuana. Stigma among many health providers and institutions underscores the need of nonjudgmental, harm reduction interventions and public health programs. In this regard, recent release from rehab/treatment was positively associated with time to non-fatal overdose in both the univariable and multivariable analyses (professional help for drug/alcohol use was positively associated in the univariable analysis). One plausible explanation is the routine admission of PWID into compulsory drug abstinence programs. A recent study among the same sample of PWID in Tijuana found that the odds of NFOD increased by 1.76 (95% CI 1.04-2.96) for individuals reporting experience in compulsory drug abstinence programs [17]. In Mexico, compulsory drug abstinence programs can be requested by a judge or family members. In Tijuana, treatment centres operate with poor government oversight or overdose surveillance [17]. Moreover, abstinence-based treatment among persons who use opioids has been linked with increased risk of overdose potentially due to reduced tolerance after release from treatment [32]. Furthermore, the time immediately after leaving methadone treatment has been associated with increased risk for overdose [33].

Reducing risk for people who use multiple substances may also be addressed through interventions and harm reduction programs that address stimulant and benzodiazepine use. However, such programs in Tijuana and other Latin American settings are limited mainly due to funding shortages. Funding is mostly directed to injection drug use given its direct connection to HIV [30]. This context calls for actively including people who use multiple substances in harm reduction efforts with more interventions geared towards concurrent use of multiple substances (e.g. stimulants and benzodiazepines), while sustaining efforts to prevent HIV and hepatitis C virus. Expanding health-care access, including evidence-based detox programs, like the Centros de Integracion Juvenil (a national drug use treatment and prevention program), and scaling-up opioid agonist/medication-assisted treatment for people who use opioids in combination with counselling and behavioural therapies are increasingly pressing needs in Tijuana.

Limitations

We note that with respect to baseline characteristics, participants lost to follow-up over our study period were generally similar to participants retained in the study. However, they significantly differed in heroin injection frequency (daily vs. less than daily) measured at baseline, with 91% reporting daily heroin injection among retained participants and 81% reporting daily heroin injection among participants lost to follow-up. However, due to the very high portion of participants reporting daily and almost daily (2–3 days a week) drug use among all drug classes, we do not expect this difference to have any effect in our estimates.

Additionally, caution is warranted when generalising our results to other PWID populations since drug-use patterns and environmental characteristics may differ in other settings. For example, in our sample the opioid class was exclusively defined by black tar heroin consumption, which can be quite different in other drug-using contexts where powder heroin is more common. Also, while prescription opioid use was assessed in the baseline survey, less than 5% of participants reported using some type of prescription opioid and hence were not included in the analysis. Importantly, as opposed to the United States, prescription opioid misuse has not yet reached epidemic levels in Mexico [34]. Moreover, polydrug use can be assessed in other ways, like co-administration of two or more drugs in the same sitting [35]. Additional research is needed in other settings with different drug availability to replicate these polydrug-use patterns as impacting the risk of overdose.

Furthermore, drug consumption as well as health outcomes were self-reported and might be imprecise due to reliance on recall and be subject to social desirability. Regarding drug use, previous studies have shown that stigma influences non-response or underreporting of substance use [36,37]. In this case, our estimates could represent a lower bound of the differences between categories due to this underreporting. However, with such high prevalence and frequency of drug use reported, and disclosure of drug use to enrol in the study, bias due to social desirability and stigma is likely limited. Additionally, the definition of overdose provided to participants is more pertinent for opioid-related overdose and not for overdose related to other drug classes [12]. If this affected our results, it would have underestimated overdoses related to stimulants and benzodiazepines. Thus, our results would represent a lower bound of the differences between categories that could be detected. We note that our measure of polysubstance use is limited due to the survey not eliciting information on the specific benzodiazepine

used nor dosing of the drug used. Thus, we cannot know with precision if the effects of the drug combinations could be modified by dose (e.g. heroin injection) or types of benzodiazepines used.

Finally, baseline data for this study were collected before emergence of fentanyl (an opioid) in the border region, which means that the frequency of NFOD events in more recent years could be higher [38]. Further research should assess how fentanyl could change the effect of combining drug classes on NFOD among PWID, as well as how polysubstance use patterns may change for individuals who use fentanyl.

Conclusions

Polysubstance using PWID in Tijuana are at elevated risk of NFOD, with the highest risk seen among those who concurrently use opioids, stimulants and benzodiazepines. PWID in Tijuana are in a particularly challenging setting where illicit substance use is increasing and accessing treatment and harm reduction services remains difficult [15,39]. Interventions, such as scaling-up naloxone availability and medication-assisted treatment for people who use other substances in addition to opioids, are urgently needed.

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Conflict of Interest

The authors have no conflicts of interest.

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