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Illicit use of opioid substitution drugs:

Prevalence, user characteristics, and the association with non-fatal overdoses

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ABSTRACT

Background and aims: Diversion of opioid substitution drugs (OSD) is of public concern. This study examined the prevalence, frequency, and predictors of illicit OSD use in a group of injecting drug users (IDUs) and assessed if such use was associated with non-fatal overdoses.

Methods: Semi-annual cross-sectional interviews conducted in Oslo, Norway, (2006-2013), from 1,355 street-recruited IDUs. Hurdle, logistic, and multinomial regression models were employed.

Results: Overall, 27% reported illicit OSD use in the past four weeks; 16.8% methadone, 12.5% buprenorphine, and 2.9% both drugs. Almost 1/10 reported at least one non-fatal overdose in the past four weeks, and roughly 1/3 reported such experience in the past year. Use of additional drugs tended to be equally, or more prevalent among illicit OSD users than other IDUs. In terms of illicit OSD use being a risk factor for non-lethal overdoses, our results showed significant

associations only for infrequent buprenorphine use (using once or less than once per week). Other factors associated with non-fatal overdoses included age, education, homelessness, as well as the benzodiazepines, stimulants, and heroin use.

Conclusions: Users of diverted OSD may represent a high-risk population, as they used more additional drugs and used them more frequently than other IDUs. However, illicit OSD use may be less harmful than previously assumed. After accounting for an extensive set of covariates, only infrequent illicit buprenorphine use, but not methadone use, was associated with non-fatal overdoses.

Keywords: diversion; methadone; buprenorphine; injecting drug users; opioid substitution treatment

1. INTRODUCTION

Diversion and illicit use of opiate substitution drugs (OSD), such as methadone and buprenorphine, appear to be widespread in countries where opioid substitution treatment (OST) is available (Duffy et al., 2012; Roche et al., 2008; Winstock et al., 2009). Illicit OSD use is of public concern due to its potential health risks and because diversion to the black market may undermine public support and legitimacy of OST. Most studies suggest a positive association between flexible OST regimens and diversion (Ritter et al., 2005; Strang et al., 2010). For this reason, there is an argument for stricter OST regimens, including supervised OSD intake and restriction of take-home doses (Obadia et al., 2001). However, less flexible regimens may result in fewer treatment seekers and lower retention rates (Duffy et al., 2012; Pani et al., 1996). This in turn could have serious public health implications given the health risks among opioid users and OST's contribution to the reduction of such risks (Clausen et al., 2008; Darke et al., 2011; Degenhardt et al., 2011).

Deciding on a strict versus a more flexible OST regimen constitutes a difficult dilemma. Thus, a better understanding of factors associated with illicit OSD use, and in turn, how such use may contribute to adverse health outcomes is important in informing the OST debate and public policies. It is a challenging task however, as even seemingly straightforward facts must be interpreted with caution. For instance, the recent increase in OSD-related fatalities reported in many countries (EMCDDA, 2013; Lee et al., 2013) does not necessarily imply that the number of drug-related deaths had been lower without diversion. It is possible that diversion primarily influences which drugs are used without necessarily affecting the total number of drug-related fatalities; i.e. OSD use may in some cases simply replace the use of heroin or other opioids without altering the risk of overdosing. If used in a mode similar to the prescribed OST regimen, such self-substitution may potentially even lower the overdose risk. Thus, it is not altogether clear whether illicit OSD use increases overall morbidity and mortality among opioid users, and if so, to what extent. Additional information about illicit OSD use, user characteristics, and OSD-related health outcomes need to be considered.

Specifically, fatal and non-fatal overdoses are the most serious side effect of illicit OSD use. These risks appear to depend upon intake modes and concomitant drug use. For instance, injection of crushed buprenorphine tablets and methadone syrup appear riskier than oral intake, as is concomitant intake of other substances, particularly benzodiazepines (Kintz, 2001; Mégarbane et al., 2006; Nielsen et al., 2008; Renard et al., 2008). Even though buprenorphine is generally considered safer than methadone (Bernard et al., 2013; Ernst et al., 2002; Heinemann et al., 2000; Seymour et al., 2003; Vormfelde et al., 2001), there have been reported fatalities after buprenorphine snorting or injecting (Ferrant, 2011; Tracqui et al., 1998). Further, fatalities have also been reported after high-dose buprenorphine consumption regardless of intake mode, especially when combined with benzodiazepines and alcohol (Häkkinen et al., 2012; Lai et al., 2006; Schifano et al., 2005; Seldén et al., 2012). However, the question remains as to whether illicit OSD use poses an independent risk for such adverse health outcomes.

Our study contributes to the literature by providing estimates of prevalence and frequency of, as well as the factors associated with, illicit OSD use among street-recruited injecting drug users (IDUs). By investigating the correlates of illicit OSD use, we aim to contribute to a better understanding of the user profiles, and to extend previous scarce findings on this topic. Further, we specifically examined the association between the frequency of illicit methadone and buprenorphine use and one important harmful effect: non-fatal overdoses. The frequency of opioid use may influence individual OSD tolerance levels, which in turn can affect the risk for non-fatal overdoses. Non-fatal overdoses are linked to increased morbidity and risk of subsequent fatal overdoses (Darke et al., 2003). To our knowledge, this is the first report to consider the frequency of illicit OSD use when investigating these questions.

2. MATERIAL AND METHODS

2.1 Study setting

Data were drawn from a large survey (n = 1,355) of street-recruited IDUs in Norway. Norway has one of the highest rates of IDUs among problem drug users, and one of the highest reported drug-induced mortality rates in Europe (EMCDDA, 2013). The country currently has an estimated number of 7,300-10,300 active IDUs (Hordvin, 2013) in a population of approximately 5 million.

OST became nationally available through a public specialised health care programme in 1998 (Waal, 2007). Recent statistics shows a total of 7,055 registered OST users in Norway; 1,788 in Oslo (Skretting, 2014). Buprenorphine has been available since 2001 and is now prescribed for approximately 50% of OST patients, with take-home doses being a common practice (Riksheim et al., 2014). Only methadone syrup and the buprenorphine preparations Subutex and Subuxone (buprenorphine-naloxone) are available for OST in Norway (The Norwegian Pharmaceutical Product Compendium 2014). Methadone is available, but rarely used as pain medication, while buprenorphine preparations (such as Temgesic) are somewhat more commonly prescribed.

2.2 Design

Our semi-annual cross-sectional study was conducted outdoors, in close proximity to Oslo's needle exchange program (NEP) and the drug consumption room (DCR). Participants were recruited from both of these facilities, which are located next to one another. Trained research staff from The Norwegian Institute for Alcohol and Drug Research (SIRUS) recruited and interviewed participants during the opening hours two or three weeknights within a month. Interview sessions were held in March and September each year. This study used data collected between 2006 and 2013. Over the study period, the NEP facility received about 80,000 visits and distributed between 1.2 and 2 million syringes annually (*personal communication NEP 2014*). Even though the majority of needles and syringes are distributed from this NEP facility, clean injecting equipment is also available free of charge from other low threshold services such as shelters, street clinics, and the DCR.

2.3 Inclusion

Clients from the NEP and the DCR facility were approached for an interview. Current OST patients were excluded from the analytical sample, as our focus was on the illicit OSD use only. No further exclusion criteria were imposed.

2.4 Representativeness

The study sample was a convenience sample. However, we found that the age and gender distributions were similar to what has been estimated for IDUs in Norway (Bretteville-Jensen et al., 2006). The high number of needles and syringes distributed annually suggests that a large proportion of the city's IDUs were using the NEP service.

2.5 *Ethics*

The study protocol was under the jurisdiction of the Norwegian Social Science Data Services (NSD) and its Data Protection Official for Research. Even though this project involved human subjects, an equivalent of the IRB exemption was obtained from NSD because the data collected were completely anonymous and did not involve any information which could directly or indirectly be linked to individual participants. Therefore, no formal NSD submission and action was required. No monetary incentives were given for participation.

2.6 Measures

The study instrument included questions on legal and illegal substance use (alcohol, cannabis, cocaine, LSD, ecstasy, amphetamine, heroin and prescription drugs) and the number of non-fatal overdoses in the month and in the year before the interview. A non-fatal overdose was defined as an incident where the person needed assistance from others to regain consciousness, while frequent drug use was defined as using on a daily, or almost daily, basis. In addition, we recorded participants' age, gender, education, current living situation, length of injecting career, treatment experience, and sources of income (including from illegal activities) for the four weeks prior to the interview.

2.7 *Data analyses*

The frequency of illegal OSD use was examined using a hurdle model (Cameron et al., 2005) in which the outcome variable was assumed to be generated by two processes; one concerning zeroes (i.e., whether illicit OSD use has occurred or not, estimated through a logistic regression model) and one concerning counts (i.e., the frequency of use, estimated through a zero-truncated negative binomial (ZTNB) model). For these analyses, the ordinally-coded illicit OSD use

variables were recoded to reflect the actual number of use days per month; e.g., those having used “once per week” were assigned 4 days/month use, those having used “2-3 times per week” were assigned a midpoint of 10 days/month use, etc. The identical set of substantive predictors was included in both parts of the hurdle model.

Next, both a logistic and a multinomial logistic model were used to examine associations between illicit OSD use and non-fatal overdoses. In the logistic model, the outcome categories were no overdoses vs. any overdose, whereas in the multinomial model the outcome categories were no overdoses (coded “0”); one overdose (coded “1”); and more than one overdose (coded “2”) in the past month. Based on the literature, we controlled for individual characteristics, previous experience of non-fatal overdoses, variables pertaining to drug usage pattern, and a dichotomous drug dealing indicator (dealing in the past four weeks) of drug accessibility.

Because study participation was completely anonymous, some participants may have been interviewed more than once, thus violating the basic assumptions of regression analyses. To account for this possible violation, the variables of “gender”, “age”, “educational level”, “age at first injection”, “type of drug at first injection”, “how heroin was used the first time” and “age at first heroin smoking” were compared in order to detect possible duplicates prior to running the analyses. The procedure uncovered 36 possible duplicates (2.6% of the total sample) and their removal did not significantly impact hereby reported results. Therefore, we reported the findings based on the entire sample. Please see (Gjersing & Bretteville-Jensen, 2013) for more information on the effects of possible duplicates.

3. RESULTS

3.1 Characteristics of the sample

Sample characteristics are shown in Table 1. Illicit use of OSD was relatively common, with 27% of the sample (n = 1,355) reporting such use. The majority used methadone (16.8%), followed by buprenorphine (12.5%), while 39 participants (2.9%) reported having used both substances during the previous month. Almost one in ten had experienced at least one non-fatal overdose within previous four weeks, while approximately one in three reported such experiences in the 12 months prior to the interview.

Participants were on average 37 years old, and slightly more likely to be male (54%). Almost one in three participants (30%) was homeless or shelter user, 61% had injected drugs for more than 10 years, and 31% were previous OST patients. Frequent and extensive drug use was common: 72% were heroin injectors averaging 3.2 injections per day, 0.28 grams (not purity-adjusted) per injection, and 24 grams monthly consumption. Frequent (daily or almost daily) use of stimulants (amphetamine and/or cocaine) was reported by 38% of the sample, while two out of three participants used benzodiazepines during the four weeks prior to the interview. Beyond heroin, methadone or buprenorphine, the participants used an average of 2.6 additional drugs (stimulants, alcohol, cannabis or benzodiazepines) in the previous month.

Compared to non-OSD users, illicit methadone users were less likely to have a shorter drug career. Further, they were more likely to have previously been an OST patient, to have made money through drug dealing, to have ever smoked heroin, to have injected heroin in the previous month, and to have injected it more frequently (Table 1, column 2-3). The total number of drugs used in addition to any opioids was also slightly higher for illicit methadone users (2.75 versus 2.48). Like illicit buprenorphine users (Table 1, column 4), a higher proportion of illicit methadone users reported frequent use of stimulants and benzodiazepines use compared to non-OSD users. Illicit buprenorphine users, however, were more likely to have experienced a non-fatal overdose, to be

younger, to have a shorter injecting career and fewer heroin-injecting days in the previous month than the non-OSD users. Still, there was a higher proportion reporting heroin injection among illicit buprenorphine users than among the non-OSD users.

Illicit use of buprenorphine was more common among those who experienced an overdose in the previous month compared to participants without this experience (20.3% vs 11.7%), while there was no difference in methadone use (column 5-6, Table 1). Also, those who experienced a non-fatal overdose recently were more likely to be younger, to be homeless/shelter users and to have had a somewhat longer drug injecting career. There was no group difference with regard to overdose experience during the *past year*. However, participants with non-fatal overdose experience reported significantly higher levels of drug use. They were more likely to have injected heroin and done so more frequently in the past four weeks and a higher proportion had also smoked the drug. Further, the mean number of additional drugs to any opioid use was significantly higher, as were the proportion that reported frequent stimulant and benzodiazepines use (50.8% vs.36.9% and 82.8% vs. 66.4%, respectively, all p's < .01).

3.2 Multivariate analyses – predictors of illicit OSD use

Results from the hurdle models separately estimating illicit methadone and buprenorphine use are presented in Table 2. Columns 1-2 show the odd ratios for use/non-use of OSDs, while columns 3-4 show the coefficients from the ZTNB regression estimating the frequency of illicit OSD use among users. While all drug use variables were significantly associated with illicit methadone use, only heroin and benzodiazepine use were associated with such buprenorphine use (see Table 2, columns 1-2). Frequent use of alcohol and cannabis was associated with lowered, while frequent use of stimulants, benzodiazepine use, heroin smoking, and recent overdose were all associated with increased likelihood of illicit methadone use. Heroin and benzodiazepine use, having been an OST patient, and an IDU career of more than 10 years were all associated with increased likelihood of illicit buprenorphine use.

Columns 3-4 (Table 2) show that frequency of illicit methadone use increased with longer IDU career and with frequent alcohol and cannabis use, but it decreased with heroin smoking. Being male was a risk factor for frequent illicit buprenorphine use, but frequent heroin use was associated with less frequent

use. Non-fatal overdose experience in the past four weeks had the opposite effect on illicit OSD use; it was associated with fewer methadone, but more buprenorphine using days. Thus, the predictors of illicit OSD use frequency differed from that of the OSD use/non-use decision.

3.3 Multivariate analyses – predictors of non-fatal overdose

Table 3 presents results from the logistic (Column 1) and the multinomial logistic (Column 2-3) regressions estimating the number of non-fatal overdoses as a function of illicit OSD and other drug use. When the outcome was operationalized as a binary overdose/no-overdose variable, as expected, heroin use was positively associated with non-fatal overdoses (see Column 1). In terms of the role of illicit OSD use, infrequent illicit use of buprenorphine was associated with an increased risk of non-fatal overdoses. Illicit methadone use however, irrespective of frequency, was not associated with such a risk. Finally, being younger, more educated, homeless, and frequent user of benzodiazepines and stimulants also were associated with increased risk for non-fatal overdose.

When comparing the non-overdose group to those who had experienced one or more than one overdose, respectively (see Columns 2-3, multinomial regression results), the illicit OSD use was associated only with an increased overdose risk for the former. Such a pattern suggests that the results obtained from the logistic regression were in most cases driven by the subsample of individuals with one non-fatal overdose.

4. DISCUSSION

OST is an effective way of reducing opioid-related harms to dependent individuals and the society (Degenhardt et al., 2009; Strang et al., 2010). However, diversion of OSD to the black market is one side effect of such programs. Our findings suggest diversion being fairly common among IDUs in our sample, as about one in four participants reported illicit OSD use within the last four weeks. Previous research has reported a wide range of estimates for illicit OSD use among IDUs. Estimates of illicit buprenorphine use range from 9% to 41% in US samples (Bazazi et al., 2011; Genberg et al., 2013), to 73% reported in a Finnish sample (where buprenorphine is the most commonly used illegal opiate) (Alho et al., 2007). In terms of illicit methadone use, a US-based study

reported a 16% rate of street methadone use over the last six months (Mitchell et al., 2009), while an Australian study reported a decline in recent methadone injecting from 31% to 13% during the relatively short time period (1997-2000) (Darke et al., 2002).

The first set of analyses (Table 1), investigating prevalence and correlates of illicit OSD use shows that the use of other illicit drugs (heroin, stimulants, and benzodiazepines in particular) was equally or even more prominent among illicit OSD users than among the remaining IDUs. This suggests that the illicit OSD users may represent a particularly high-risk user profile, and that illegally obtained methadone and buprenorphine were likely used in addition to, rather than instead of, other substances. For example, the overall heroin use patterns were generally more severe among the illicit OSD-users, suggesting that the diverted OSDs were not necessarily used as a heroin substitute, but instead as an additional substance. Viewed in isolation, this could lead to the conclusion that illicit OSD use increases the risk of non-fatal overdoses. The fact that those who recently experienced a non-fatal overdose also reported higher illicit buprenorphine use further supports this notion.

The multivariate analysis (Table 2) confirmed that illicit OSD use was predicted by the use of several additional drugs (heroin and benzodiazepines in particular), as well as by having a longer drug career and having been an OST patient. This is congruent with previous findings from other studies (Genberg et al., 2013; Jenkinson et al., 2005; Nielsen et al., 2007; Ompad et al., 2008; Vlahov et al., 2007). However, contrary to previous research, we did not find demographic or socioeconomic factors to be predictive of illicit OSD use in our sample, which may be due to the unique social circumstances in Norway (where the SES differences are smaller than in many other Western countries).

The increased health risk posed by multidrug use is well established in the pharmacological literature, and simultaneous use of other drugs is usually involved in OSD-related deaths (Häkkinen et al., 2012; Kintz, 2001; McCance-Katz et al., 2010; Pirnay et al., 2004). In accordance with previous research (Daniulaityte et al., 2012; Jenkinson et al., 2005; Nielsen et al., 2007; Obadia et al., 2001), our findings show that such concerted drug use is also common among the broader group of IDUs. We investigated whether illicit OSD use is an independent risk factor for non-lethal overdose. The results shown in Table 3 document a positive association between low-frequency use of illicit buprenorphine and non-fatal overdoses, whilst more frequent buprenorphine use, or

methadone use at any frequency, was not associated with increased risk for non-fatal overdose. This was in contrast to our expectations and findings from previous studies (Lee et al., 2013; Nielsen et al., 2008; Nielsen et al., 2007).

Such findings are interesting and quite puzzling, especially as there has been an increase in methadone-related deaths in Norway during the same time period as our investigation (Bernard et al., 2013). The positive association of illicit buprenorphine use and overdose risk may be explained by the patterns of use and/or the methods of drug intake. Crushed buprenorphine tablets could for instance be more commonly injected than methadone syrup, which is assumed to be a more hazardous intake method. Different intake modes may in turn be related to motives for use, such as the removal of withdrawal symptoms versus getting "high" (Daniulaityte et al., 2012; Harris et al., 2013; Ison et al., 2006; Otiashvili et al., 2010). Further, that a low frequency of buprenorphine use was associated with increased overdose risk could potentially be explained by low tolerance levels in those who use buprenorphine infrequently, as tolerance levels are considered an important mechanism in relation to drug overdoses (Darke et al., 1996; Seldén et al., 2012). Furthermore, previous literature has documented the risk of buprenorphine injecting in relation to non-lethal overdoses (Häkkinen et al., 2012; Nielsen et al., 2007), especially in high-doses and when combined with benzodiazepines and alcohol (Häkkinen et al., 2012; Lai et al., 2006; Schifano et al., 2005; Seldén et al., 2012). To discourage injecting some treatment programmes prefer to prescribe the combined buprenorphine-naltrexone formulation (Riksheim 2014). Unfortunately, information on the type of buprenorphine used was not available for this sample. Our results are consistent with the possibility of overdoses resulting from the combined use of buprenorphine and benzodiazepines, although the synergistic effects could not be fully explored here.

Thus, our results suggest that illicit OSD use is an independent risk for non-lethal overdose, albeit for infrequent buprenorphine use only. Whether it implies an overall increased health risk, however, depends on the counterfactual of what the alternatives to the illicit OSD intake would be, both in terms of the drug consumption patterns and intake modes.

4.1 Limitations and strengths of our study

To fully understand the role of illicit buprenorphine use in relation to non-lethal overdoses additional information, like simultaneous use of other drugs, individual opioid tolerance levels, and motives for use at the time of the overdose incidence, would be required. For example, self-medication of withdrawal symptoms may pose a lower health risk than injecting buprenorphine to get "high". No study has so far had access to such comprehensive data sets. As in other studies using self-reported data, weaknesses such as recall bias and under- and over-reporting are possible. Although most questions related to recent behaviours, the disorganized lifestyle and frequent intoxications among the study participants may have resulted in imprecise reporting. However, it could be argued that life threatening incidents, such as an overdose, would be remembered and reported with a large degree of precision. Further, our study focused on only one of many health risks potentially associated with illicit OSD use. Furthermore, although the occurrence of non-fatal overdoses is found to increase the risk of fatal overdoses (Darke et al., 2011; Stoove et al., 2009), it is possible that our findings are not directly transferable to such situations. For example, selection mechanisms may be at play if buprenorphine use is associated not only with a higher risk of non-fatal overdoses but also with an overall higher mortality risk. It may also be that an overdose from methadone is more likely to have a fatal outcome compared to overdose from buprenorphine. This could result in a competing risks bias or a Neyman bias, impacting our estimates. Finally, while unobserved heterogeneity and possible type-2 errors should be acknowledged, the results nevertheless provided suggestive preliminary evidence on a poorly understood phenomenon.

Our study included a rich set of covariates and had a relatively large sample of street-recruited IDUs who were expected to be at high-risk for illicit OSD use. In addition, it is likely that our data collection location allowed us to recruit participants from a broader spectrum of IDUs than might have been available from alternative recruitment locations, such as treatment centres or prisons. Finally, detailed frequency information allowed us to explore how the risk non-fatal overdoses varied by intensity of use of OSD, heroin and stimulants in relation to other drugs, personal characteristics and experiences.

4.2 Conclusion

Diversion of OSD has been of great public concern for some time. Given the recurring debate concerning the nature of OST regimens and their implications on treatment seeking and retention, improved knowledge on potentially adverse consequences of OST diversion is crucial. Our preliminary findings suggest that illicit use of OSD may be less harmful than previously assumed. After controlling for an extensive set of covariates, only infrequent illicit use of buprenorphine was associated with an increased risk of non-fatal overdose, whereas illicit methadone use was not associated with such a risk. Such somewhat unexpected results may stem from different ways of administering and consuming these two drugs, different motives for use, lack of buprenorphine tolerance or from the synergistic effects of additional drug use (such as heroin, benzodiazepines, and stimulants). Further research, both qualitative and quantitative, is needed to explore motivational factors, intake patterns, and other health outcomes among illicit OSD users in order to understand the full consequences of OSD diversion.

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Table 1 Characteristics of the study population (n=1,355), and subdivided by illicit OSD use and by non-fatal overdose experience in the past four weeks

	Full sample N = 1355	Division by illicit OSD use			Division by non-fatal overdose experience	
		Non OSD users n = 998	Methadone users n = 227	Buprenorp. users n = 169	Overdose (No) n = 1227	Overdose (Yes) n = 128
Dependent variables						
Use of OSD (%)	26.6	-	-	-	25.7	32.8
Use of subutex/suboxone[1] (%)	12.5	-	17.2	-	11.7	**20.3****
Use of methadone (%)	16.8	-	-	23.8	16.7	17.2
Non-fatal overdose last month (%)	9.4	8.6	9.7	**15.4****	-	-
Personal characteristics						
Male (%)	53.9	52.9	56.8	57.4	54.4	48.4
Age (M, sd)	36.6 (10.0)	37.3 (10.1)	36.0 (8.9)	**32.6***** (10.2)	37.0 (10.0)	**33.2***** (9.7)
≥ Mandatory years of education (%)	64.0	63.7	66.1	61.5	63.3	70.3
Currently homeless/shelter user (%)	29.5	29.5	33.5	27.2	27.7	**47.7*****
IDU 1-5 years (%)	18.0	18.9	**8.4*****	**26.0***	17.8	20.3
IDU 6-10 years (%)	17.6	16.2	20.7	**26.0****	16.8	**25.8***
IDU more than 10 years (%)	60.6	61.2	67.8	**43.2*****	61.4	53.1
Previous OST patient (%)	31.2	28.1	**43.2*****	33.1	30.5	38.3
Non-fatal overdose last year (%)	30.8	31.1	26.9	33.1	31.5	24.2
Drug dealing (%)	35.6	33.5	**44.9****	35.5	35.0	41.4
Drug use						
Buprenorphine:						
No use	87.5	-	82.8	-	88.4	**79.6*****
Up to once a week	6.1	-	11.0	48.5	5.3	**13.3*****
Two to three days per week	2.9	-	4.0	23.1	2.6	5.5
Almost daily to daily	3.5	-	2.2	28.4	3.7	1.6
Methadone:						

No use	83.2	-	-	76.8	83.3	82.8
Up to once a week	10.8	-	64.3	17.8	10.5	13.3
Two to three days per week	2.1	-	12.8	3.0	2.1	2.3
Almost daily to daily	3.8	-	22.9	2.4	4.1	1.6
Injecting heroin:						
No use	28.3	33.8	**7.0*** **	**20.1*** **	30.1	**10.9*** **
Up to once a week	9.3	6.8	**13.2** **	**23.1*** **	9.0	12.5
Two to three days per week	4.8	3.9	6.2	**10.1*** **	4.6	6.3
Almost daily to daily	57.6	55.5	**73.6*** **	**46.7***	56.3	**70.3** **
Injected heroin last month (%)	71.7	66.2	**93.0*** **	**79.9*** **	69.9	**89.1*** **
Ever smoked heroin (%)	71.0	67.5	**78.9** **	**84.0*** **	69.4	**85.9*** **
No. of heroin injections per day (M, sd)	3.2 (1.7)	3.2 (1.7)	3.1 (1.7)	**2.7** ** (1.8)	3.1 (1.7)	3.4 (2.0)
Grams of heroin per injection (M, sd)	0.28 (0.16)	0.29 (0.16)	0.29 (0.16)	**0.24** ** (0.12)	0.28 (0.16)	0.28 (0.16)
Total monthly heroin use (grams; M, sd)	24.2 (26.2)	25.6 (27.1)	23.9 (25.1)	**15.1*** ** (19.5)	24.2 (26.4)	24.0 (24.3)
Freq use of stimulants (%)	38.2	35.8	**46.3** **	**45.6***	36.9	**50.8** **
Freq. use of alcohol (%)	8.6	8.3	11.5	8.3	8.4	10.9
Freq. use of cannabis (%)	33.3	32.3	34.4	38.5	33.0	35.9
Use of benzodiazepines (%)	68.0	63.2	**81.5*** **	**81.1*** **	66.4	**82.8*** **
No. of additional drugs (M, sd)[2]	2.55 (1.04)	2.48 (1.02)	**2.75*** ** (1.08)	**2.74** ** (1.09)	2.52 (1.04)	**2.78** ** (0.94)
Interviewed 2010-2013 (%)	54.0	53.1	53.7	58.6	54.2	52.3

Group differences were tested using proportion tests and t-tests: * $p<0.05$; ** $p<0.01$; *** $p<0.001$.

Comparisons involved non-OSD users vs. methadone users (column 2 vs. column 3) and non-OSD users vs. buprenorphine users (column 2 vs. column 4). Further, participants with recent non-fatal overdose experience were compared to participants without such experience (column 5 vs. column 6).

[1]Subutex and Subuxone are both buprenorphine preparations.

[2] The number of drugs taken in addition to any opioid use in the previous month (stimulants, alcohol, cannabis and benzodiazepines).

Table 2 Illicit OSD use within the past four weeks, hurdle model, n = 1,355.

	Odds ratio from the logistic regression		Coefficients from the zero truncated negative binominal (ZTNB) regression[1]	
	Methadone use	**Buprenorphine use**	**Methadone use**	**Buprenorphine use**
Personal Characteristics and Experiences				
Gender (Male)	0.957 [0.260]	0.561 [0.174]	1.996 [1.743]	**8.570*** ** [2.167]
Age:				
< 30	1	1		
30-39	0.946 [0.369]	0.749 [0.312]	-1.532 [2.194]	-4.589 [2.971]
40+	0.682 [0.285]	0.664 [0.258]	-0.688 [2.778]	-2.768 [3.134]
Greater than mandatory education (yes/no)	0.855 [0.213]	1.232 [0.386]	1.968 [1.633]	-2.707 [2.275]
Homeless/shelter user (yes/no)	0.861 [0.215]	1.059 [0.344]	0.473 [1.704]	-3.021 [2.267]
IDU career length:				
1-5 years IDU	1	1		
6-10 years IDU	0.964 [0.530]	0.950 [0.367]	**7.571** ** [2.845]	0.697 [2.483]
10+ years IDU	0.828 [0.318]	**0.408*** [0.151]	**10.354*** ** [2.375]	1.909 [2.937]
Previous OST patient (yes/no)	1.391 [0.421]	**1.960*** [0.636]	0.253 [1.955]	-2.160 [2.428]
Dealing last month (yes/no)	1.444 [0.374]	0.509 [0.184]	0.075 [1.816]	2.778 [2.370]
Non-fatal OD last month (yes/no)	**1.685*** [0.410]	1.132 [0.298]	**-5.383*** [2.104]	**5.542*** [2.277]
Opioid Use				
Heroin use:				
No use	1	1		
Up to once a week	**4.199** ** [1.971]	**3.364*** [1.643]	2.739 [5.901]	-2.731 [3.971]
Two to three days per week	**3.627*** [1.862]	**12.743*** [14.37]	3.121 [6.430]	-7.048 [4.920]
Almost daily to daily	**4.423*** ** [1.373]	1.837 [0.617]	-1.276 [5.644]	**-13.92*** ** [3.583]
Heroin smoking (yes/no)	**2.457*** ** [0.612]	1.531 [0.421]	**-9.615** ** [3.299]	3.004 [2.749]
Use of Other Drugs				
≥ Almost daily to daily alc./cann. use (yes/no)	**0.613** ** [0.113]	1.125 [0.258]	**4.942** ** [1.537]	1.116 [1.796]
Use of benzodiazepines (yes/no)	**2.010*** [0.571]	**3.147** ** [1.156]	0.027 [2.445]	-3.324 [3.112]
Time				
Interviewed in 2010-2013 (yes/no)	0.818 [0.231]	1.610 [0.456]	1.989 [1.902]	-1.658 [2.305]

Standard errors in brackets.

* p<0.05; ** p<0.01; *** p<0.001.

[1] The ordinally coded dependent variables were re-coded to reflect the actual number of use days per month: “No use in the last four week” (=0 days), “Less than once a week” (=2 days), “Once a week” (=4 days), “Two to three days per week” (=10 days), “Almost daily” (=20 days), and “Daily” (=30 days).

Table 3 Non-fatal overdoses in the past 4 weeks, logistic (Model 1) and multinomial logistic model[1] (Model 2), odds ratios (OR) and relative risk ratios (RRR), n = 1,355.

	Model 1 **Logistic**	*Model 2* **Multinomial logistic**	
		1 overdose	**≥ 2 overdoses**
	OR	**RRR** (n = 86)	**RRR** (n = 42)
Personal Characteristics and Experiences			
Gender (Male)	0.843 [0.188]	0.925 [0.250]	0.721 [0.261]
Age:			
< 30	1	1	1
30-39	**0.574*** [0.156]	0.641 [0.206]	0.438 [0.206]
40+	**0.458*** [0.143]	**0.445*** [0.169]	0.464 [0.235]
Greater than mandatory education (yes/no)	**1.616*** [0.345]	**1.680*** [0.430]	1.471 [0.518]
Homeless/shelter user (yes/no)	**2.199***** [0.438]	**2.145**** [0.511]	**2.365**** [0.775]
IDU career length:			
1-5 years IDU	1	1	1
6-10 years IDU	1.390 [0.412]	1.115 [0.393]	2.169 [1.084]
10+ years ISU	1.320 [0.411]	1.158 [0.422]	1.805 [0.993]
Previous OST patient (yes/no)	1.335 [0.292]	1.344 [0.347]	1.308 [0.486]
Non-fatal overdose in previous year (yes/no)	0.698 [0.167]	**0.521*** [0.159]	1.147 [0.422]
Opioid Use			
Buprenorphine use:			
No use	1	1	1
Up to once a week	**2.226*** [0.720]	**2.345*** [0.880]	1.893 [1.026]
Two to three days per week	1.881 [0.874]	2.446 [1.226]	0.796 [0.850]
Daily to almost daily	0.465 [0.352]	0.720 [0.554]	0.000 [0.001]
Methadone use:			
No use	1	1	1
Up to once a week	0.699 [0.210]	0.719 [0.252]	0.648 [0.334]
Two to three days per week	0.575 [0.376]	0.555 [0.436]	0.620 [0.665]
Daily to almost daily	0.307 [0.230]	0.214 [0.222]	0.562 [0.589]
Heroin use:			
No use	1	1	1
Up to once a week	**2.531*** [1.071]	**4.306**** [2.262]	0.707 [0.600]
Two to three days per week	2.460 [1.262]	2.995 [1.968]	1.912 [1.472]
Daily to almost daily	**2.458**** [0.825]	**3.433**** [1.555]	1.461 [0.726]
Use of Other Drugs			
Use of benzodiazepine (yes/no)	**1.677*** [0.431]	**1.884*** [0.606]	1.381 [0.561]
≥ Almost daily/daily use of alc/cann (yes/no)	1.354 [0.232]	1.398 [0.284]	1.287 [0.365]
≥ Almost daily to daily use of stimulants (yes/no)	**1.617*** [0.321]	1.338 [0.319]	**2.371**** [0.787]
Time			

[1] An additional analysis (not shown) using a simple use/non-use dummy for illicit methadone and buprenorphine use gave the same result; buprenorphine use was significantly and positively associated with a higher risk of having experienced a non-fatal overdose, while the association with methadone was not statistically significant. Further, analyses based on a subset of respondents (for whom such data were available) accounting for the use of pharmaceutical opioids revealed no significant association with non-fatal overdoses. The models' main results remained unchanged.

Interviewed in 2010-2013 (yes/no)	0.826 [0.178]	0.110 [0.239]	0.706 [0.245]

Standard errors in brackets.
* p<0.05; ** p<0.01; *** p<0.001