

Research Paper

Overdose mortality rates in Croatia and factors associated with self-reported drug overdose among persons who inject drugs in three Croatian cities

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ABSTRACT

Background: Drug overdose is the major cause of morbidity and mortality among persons who inject drugs (PWID). We assessed factors associated with the non-fatal drug overdose among PWID in three Croatian cities and national trends of overdose-related mortality (OM), and rates of uptake of opioid agonist drug treatment (OAT).

Methods: We used a respondent-driven sampling method to recruit 830 PWID in Zagreb, Split and Rijeka in 2014/2015. Participants completed behavioural questionnaires that included questions about overdose history, and we used Poisson regression to assess factors associated with self-reported overdose. We used joinpoint regression to calculate national trends of OM from 2001 to 2015 and rates of uptake of drug treatment from 2005 to 2015.

Results: Lifetime prevalence of self-reported drug overdose in our RDS sample was 45.2%, while 4.1% of PWID reported overdose in the past 12 months; PWID who injected more than one type of drug in the past 12 months (adjusted prevalence ratio [aPR] = 4.56, 95% confidence intervals [CI] = 1.35–15.38) compared to injecting only heroin, and those enrolled in OAT (aPR = 1.94, 95% CI = 1.01–3.74) were more likely to report overdose in the past 12 months. We observed an increase in annual percent change (APC) of the national OM rates from 2001 to 2007 (APC = 22.5%, 95% CI = 16.3–29.0) and a decline from 2007 to 2015 (APC = –8.0%, 95% CI = –5.3– –10.5). The national rates of drug treatment enrollment increased from 2005 to 2010 (APC = 12.0%, 95% CI = 10.3–13.8), mostly due to increase in provision of buprenorphine from 2005 to 2008 (APC = 130.4%, 95% CI = 102.1–162.7).

Conclusion: Injecting more than one type of drugs and enrollment in OAT while still injecting drugs was positively associated with non-fatal overdose in our sample. To further reduce OM in Croatia we suggest improvements in coverage and delivery of OAT and establishment of provision of naloxone for PWID.

Introduction

Although the majority of cases of drug overdose in persons who inject drugs (PWID) do not result in death, overdose is the major cause of mortality among PWID (EMCDDA, 2017a). In 2014, opioid users in Europe were 5 to 10 times more likely to die than their peers of the same age and gender (EMCDDA, 2017a). It is estimated that 8,441 overdose deaths occurred in the European Union (E.U.), Norway and Turkey in 2015, a 6% increase compared to 2014 and the third

consecutive year with an observed increase (EMCDDA, 2017a). This corresponds to an overdose mortality rate of 20 per million population aged 15–64 years in Europe, and 19 per million population in Croatia (total of 54 deaths) (EMCDDA, 2017a). Available, though limited, evidence on the occurrence of a non-fatal overdose in PWID in Central and Eastern Europe suggests that it is a frequent and important cause of morbidity and mortality for PWID (Gilbert et al., 2013; Makarenko et al., 2017; Uusküla et al., 2015). Increase in the overdose-related deaths was even higher in the United States of America (U.S.), where

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due to a staggering increase in the use of prescription opioids and the emergence of highly potent synthetic opioids such as fentanyl and its derivatives (Compton, Jones, & Baldwin, 2016; Humphreys, 2017), overdose deaths nearly tripled from 1999 to 2014 with overdose mortality of 163 per million population in 2016 (Rudd, Aleshire, Zibbell, & Gladden, 2016).

The majority of cases of overdose among PWID are due to heroin use, but overdoses can also occur as a consequence of the non-medical use of opioid agonist treatment (OAT) medications, such as methadone or buprenorphine, or other opioid pain medications (EMCDDA, 2017b). The risk of overdose is increased in those who re-start opiate use after a period of abstinence, for example after discharge from drug-free treatment or after release from prison (Darke & Hall, 2003; Strang, 2015). Non-fatal overdose is associated with considerable morbidity (including aspiration pneumonia, cognitive impairment, renal failure, hearing loss and injuries from falling) and increased risk for subsequent fatal overdose (Caudarella et al., 2016; Darke, Mills, Ross, & Teesson, 2011).

The mortality multiplier study in 2015 estimated the overall population of high-risk opioid users in Croatia to be 8,874 (95% confidence intervals [CI] 7,200–11,574), out of which 6,344 (95% CI: 5,147–8,255) were PWID (EMCDDA, 2018). These estimates represent a 11% decline compared to 2012, when estimated 10,012 high-risk opioid users lived in Croatia (EMCDDA, 2013).

Available pharmacological options for opioid addiction treatment in Croatia are methadone, buprenorphine and Suboxone and they are predominantly administered thru outpatient service (EMCDDA, 2018). Outpatient treatment is organized through a network of services for mental health promotion and dependence prevention at county institutes of public health. OAT is prescribed by specialized office-based medical doctors (e.g. psychiatrists) or by specialized addiction treatment centers, while on the daily basis OAT is predominantly administered thru outpatient service by general practitioners who are issuing prescriptions and dispensing medications. Other means of treatment of drug use disorders available in Croatia are hospital-based inpatient treatment and therapeutic communities (Croatian Institute of Public Health, 2016). The costs of the OAT are covered by the Croatian Institute for Health Insurance.

Opioid overdose can be treated by administration of naloxone, an opioid antagonist, which can safely reverse the effect of opioids if administered in time (Kim & Nelson, 2015). However, access to naloxone in Croatia is limited to medical settings, including ambulances, and is not available to people likely to witness an opioid overdose, such as PWID or their friends and families.

PWID recruited thru respondent-driven sampling (RDS) surveys in three Croatian cities in 2015 reported opioids as the most commonly injected drugs in the past month (heroin in Split and Rijeka and methadone in Zagreb) with high levels of methadone and buprenorphine misuse (Handanagic, Sevic et al., 2016). In 2013, 48% of all reported overdose deaths were assigned to methadone overdose and 23% to heroin overdose (Office for Prevention of Drug Abuse of the Republic of Croatia, 2016).

Due to the increase in the overdose-related deaths in Europe and globally, and widespread high risk injecting behaviours reported by PWID in three Croatian cities, this paper aimed to assess (1) factors associated with the self-reported non-fatal drug overdose among PWID recruited by RDS in Zagreb, Split and Rijeka, (2) national trends of OM rates and (3) national rates of uptake of drug treatment. To our knowledge, this is the first study exploring these issues in Croatia.

Methods

Recruitment

From November 2014 to February 2015 we conducted bio-behavioural surveys among PWID in three Croatian cities (Zagreb, Split and Rijeka) using RDS - a chain referral sampling method that is globally

accepted and commonly used to sample hard-to-reach populations at risk for HIV (Heckathorn, 1997; Johnston et al., 2016). In RDS, recruitment starts with limited number of initial recruits (“seeds”) who are non-randomly chosen by researchers. Each participant receives up to three coupons that they can use to recruit their peers. Persons were eligible to participate in the survey if they injected drugs in the previous month, were 18 or more years old, were residents of the city where the survey was conducted, had a valid recruitment coupon and provided an oral informed consent. Trained interviewers administered a standardized behavioural questionnaire. Participants received monetary compensation for their time. Participation in the surveys was voluntary and anonymous. A detailed description of the RDS methodology for each survey was published elsewhere (Handanagic, Bozicevic et al., 2016; Handanagic, Sevic et al., 2016).

We recruited 830 PWID (176 from Zagreb, 255 from Rijeka and 399 from Split), with a response rate of 37.7%.¹ Table 1 shows that the majority of PWID in our sample were older than 30 years (77.1%), male (77.6%), with the primary school or lower education (84.0%), injecting for 11 years or more (73.3%), with the median monthly income of \$234 USD.² Needle and syringe exchange programmes (NSEP) were the main source of needles and syringes in the past month for 61.8% of PWID, while 26.6% were enrolled in OAT at the time of the survey.

Measures

We assessed socio-demographic characteristics, history of non-fatal drug overdose during participants’ lifetime and in the past 12 months, drugs used, and circumstances related to the last non-fatal overdose, and utilization of OAT and NSEP in the past 12 months. We divided monthly income into three categories (\leq \$156 USD, \$157–\$468 USD and \geq \$469 USD), and length of injection drug use into two categories (\leq 10 years and \geq 11 years) based on the distribution of these variables in the sample. Additionally, we categorized drugs injected in the past 12 months into four categories: 1) more than one type of drug, 2) only methadone or buprenorphine, 2) only heroin and 4) only stimulants (cocaine, crack, amphetamine or methamphetamine).

Data analysis of RDS surveys

For categorical variables, we reported unweighted sample proportions, while for continuous variables we reported a median with 25th and 75th percentiles. Multiple approaches for accounting for the RDS survey design in regression analysis have been suggested (Wirtz et al., 2016). Since we aggregated data from three different RDS surveys to be able to conduct regression analysis with the rare main outcome (self-reported overdose in the past 12 months), we decided not to use RDS weights in the regression analysis. Consequently, our findings are not representative of the entire population of PWID in the included cities.

We used generalized estimating equations (GEE) and modified Poisson regression with a robust standard error (*proc genmod* function in SAS 9.4) to calculate prevalence ratios (PR) with 95% CI and two-sided p-values. To account for the specific RDS survey design and general dependence among observations, which are linked to one another in the recruitment networks, we clustered the model on the

¹ As RDS is a chain-referral recruitment method where participants recruit their peers by offering them coupons, accurate response rate is not possible to calculate because we do not know how many coupons were in reality offered to potential participants. During the survey, 830 participants received total of 2,094 recruitment coupons, and 789 participants were recruited in the survey by other participants (41 were “seeds” chosen by researchers). Therefore, 38% (789/2,094) of all given coupons were returned, and approximate non-response rate was 62%.

² United States Dollars. 1 USD = 6.41 HRK (*Hrvatska Kuna*) – based on the average exchange rate for the period of the survey duration. In 2015, the average monthly salary after tax in Croatia was 5,711 HRK or \$890 USD.

Table 1
Sample characteristics, overdose history and drug use among persons who inject drugs (PWID) in three Croatian cities, 2014–2015.

	n/N (%)
Age in years	N = 830
Median	36
25 th percentile-75 th percentile	30-43
18-29	189 (22.9%)
≥ 30	636 (77.1%)
Gender	
Male	634 (77.6%)
Female	183 (22.4%)
Education	
Primary school or lower	694 (84.0%)
Secondary school or higher	132 (16.0%)
City of residence	
Zagreb	176 (21.2%)
Rijeka	255 (30.7%)
Split	399 (48.1%)
Length of injection drug use in years	
Median	17.0
25 th percentile-75 th percentile	10-23
≤ 10	222 (26.7%)
≥ 11	609 (73.3%)
Monthly income in USD ^a	
Median	\$234
25 th percentile-75 th percentile	\$78-\$468
\$0-\$156	473 (56.9%)
\$157-\$468	190 (23.0%)
≥ \$469	159 (19.1%)
Drugs injected in the past 12 months	N = 825
Combination of any two types of drugs	449 (54.4%)
Only methadone or buprenorphine	173 (21.0%)
Only heroin	146 (17.7%)
Only stimulants ^b	57 (6.9%)
Currently enrolled in opioid agonist treatment (OAT)	221/830 (26.6%)
NSEP ^c was the main source of needles and syringes in the past month	472/764 (61.8%)
Ever witnessed an overdose	564/830 (67.9%)
Last time participants witnessed an overdose they ^d :	N = 561
Called emergency medical services	422 (75.2%)
Tried to wake the person with physical stimulation	330 (58.9%)
Performed first aid or cardiopulmonary resuscitation	181 (32.3%)
Injected stimulant ^b drugs or water and salt	159 (28.3%)
Took the person to the hospital	34 (6.1%)
Injected naloxone ^e	5 (0.9%)
Did nothing	2 (0.4%)
Other	21 (3.7%)
Ever overdosed	373/825 (45.2%)
Lifetime frequency of overdose	
Median	2.0
25 th percentile-75 th percentile	1-4
Overdosed more than once in the lifetime	252/354 (71.2%)
Received emergency medical treatment during the last overdose	269/373 (73.5%)
Substances used during the last overdose ^d :	N = 370
Heroin	274 (74.5%)
Alcohol	81 (21.9%)
Benzodiazepine	49 (13.2%)
Methadone	25 (6.8%)
Cocaine or crack	26 (7.0%)
Amphetamine/methamphetamine	23 (6.2%)
Combination of heroin and cocaine or crack ("speedball")	11 (3.0%)
Buprenorphine	7 (1.9%)
Others	10 (2.7%)
Ever overdosed with the combination of opioids and other drugs or alcohol	200/369 (54.2%)
Overdosed in the past 12 months	34/826 (4.1%)

^a United States Dollars. \$1 USD = 6.41 HRK (Croatian national currency *Kuna*) – based on the average exchange rate for the period of the survey duration (November 2014-February 2015). An average monthly salary after tax in Croatia for 2015 was 5,711 HRK or \$890 USD.

^b Cocaine, crack, amphetamine or methamphetamine.

^c NSEP-Needle and syringe exchange program.

^d Multiple answers possible.

^e Antagonist of opioid receptors that can reverse effect of opioid medication

and is used in emergency treatment of opioid overdose.

recruitment chains by using *repeated subject* function in SAS 9.4 with an exchangeable correlation matrix (Zou & Donner, 2013; Zou, 2004). This approach was previously utilized in the similar settings of combined multi-site RDS surveys (Broz et al., 2014). To account for the sample inclusion probabilities and multisite design of the surveys, we included participants' self-reported social network size (defined as a number of PWID living in the city where the survey was conducted that participants know by name or nickname and they saw in the past 30 days) and city of residence as a fixed effects in the regression model. We performed analysis in SAS 9.4 University Edition (SAS Institute Inc., Cary, NC, USA).

We examined bivariable associations between self-reported overdose in the past 12 months as our main outcome, and sociodemographic characteristics, drug use behaviours and enrollment in OAT and NSEP in the past 12 months. Furthermore, in the multivariable model, we explored the associations between two independent variables of interest (a type of drugs injected in the past 12 months and enrolment in the OAT in the past 12 months) and self-reported overdose in the past 12 months. Based on the previous research we examined age, gender, education, income level, incarceration, duration of injection, drug use behaviours and enrolment in OAT and NSEP as potential confounders. We included confounders in the model if they were associated with both outcome and independent variables of interest at the level of $p \leq 0.2$. Furthermore, using backward elimination we tested the effect of each confounder on the association between the main outcome and two independent variables of interest. We kept the confounders in the final model if they changed the value of the PR between any of two independent variables of interest and the main outcome by $\geq 10\%$. The final model was adjusted for confounding for current enrolment in OAT and types of drugs injected in the past 12 months. Participants with the missing values for the main outcome, independent variables of interest or included confounders were excluded from the analysis.

Participants provided oral informed consent before participating in the survey. Ethical approval for this survey was granted by the Ethical Board of the University of Zagreb, the Ethical Board of the University Hospital for Infectious Diseases "Dr. Fran Mihaljevic", and the Ethical Board of the Croatian National Institute of Public Health.

Trend analysis of overdose-related mortality and rates of uptake of drug treatment in Croatia

Mortality data were provided by the Croatian National Bureau of Statistics (CNBS), and it included national estimates of the overdose-related deaths (X-42,³ X-62⁴ and Y-12⁵) classified according to the 10th edition of the International Statistical Classification of Diseases and Related Health Problems (ICD-10) (Croatian Bureau of Statistics, 2018). We calculated national OM rates per million population from 15 to 64 years old, using population estimates from the CNBS standardized for the age of E.U. population (Croatian Bureau of Statistics, 2018). We extracted data on the number of people treated with methadone, buprenorphine and a total number of people enrolled in any type of drug treatment from 2005 to 2015 from the reports published by the Croatian Institute for Public Health (Croatian Institute of Public Health, 2016). Furthermore, we calculated national crude rates of methadone,

³ Accidental poisoning by and exposure to narcotics and psychodysleptics (hallucinogens) including: cannabis (derivatives), cocaine, codeine, heroin, lysergide (LSD), mescaline, methadone, morphine, opium (alkaloids). (List of substances applies for X62 and Y12).

⁴ Intentional self-poisoning by and exposure to narcotics and psychodysleptics (hallucinogens).

⁵ External causes of morbidity and mortality: Poisoning by and exposure to narcotics and psychodysleptics (hallucinogens).

buprenorphine and total drug treatment uptake per million population using the population estimates of the CNBS from 2005 to 2015.

We used joinpoint regression to analyse trends of OM from 2001 to 2015 and drug treatment uptake rates from 2005 to 2015, and we reported annual percentage change (APC) with 95% CI. We considered APC to be significant if two-sided p-value for trend was less than 0.05 (Kim, Fay, Feuer, & Midthune, 2000). For this analysis, we used Surveillance Epidemiology and End Results (SEER) Joinpoint Software, version 4.5.0.1 (Statistical Methodology & Applications Branch Surveillance Research Program National Cancer Institute, 2017), and we visualized results using Microsoft Excel 2016.

Results

Table 1 shows that the majority of PWID (67.9%) in our sample reported witnessing an overdose in their lifetime, 75.5% alerted emergency medical services about the event, and one in three PWID tried to provide first aid or cardiopulmonary resuscitation in this situation. Almost half of PWID (45.2%) experienced at least one overdose episode in their lifetime, the majority of them (71.2%) reported overdosing more than once, and 73.5% reported receiving emergency medical treatment during the last overdose.

The most commonly reported drug at last overdose among PWID in our sample was heroin (74.5%), followed by benzodiazepines (13.2%), methadone (6.8%), cocaine (6.2%) and amphetamine/methamphetamine (6.2%). Approximately one in five (21.9%) PWID reported alcohol consumption at last overdose. More than half (54.2%) of PWID reported ever overdosing with a combination of opioids and some other drug. A total of 4.1% of participants in the sample reported an overdose in the past year, of which 40.6% overdosed more than once in the past year.

One in four (212/825, 25.7%) PWID in the sample reported injecting more than one type of drug in the month prior to the survey. The most common patterns of polydrug use in the past month among PWID in the sample were as follows: methadone or buprenorphine, heroin and benzodiazepines (87/212, 41.1%), at least one stimulant drug (cocaine, crack, amphetamine/methamphetamine) and heroin (46/212, 21.8%), and methadone or buprenorphine and heroin (25/212, 11.8%).

Table 2 shows results of the bivariable and multivariable regression analysis. In the bivariable analysis, the self-reported overdose in the past 12 months among PWID in the sample was marginally associated (at $p = 0.05$) with the city of residence and polydrug use in the past 12 months, and significantly associated ($p < 0.05$) with being currently enrolled in OAT. When adjusted for confounding in the final model, PWID in the sample who reported injecting more than one type of drug in the past 12 months compared to ones injecting only heroin were significantly more likely to experience non-fatal overdose in the past 12 months (aPR = 4.56, 95% CI = 1.35–15.38). When adjusted for confounding, PWID in the sample who were currently enrolled in OAT were more likely to experience overdose in the past 12 months compared to PWID not enrolled in OAT (aPR = 1.94, 95% CI = 1.01–3.74).

From 2001 to 2007 we observed a significant increase in the national OM rates (APC = 22.5%, 95% CI = 16.3–29.0), which was followed by the significant decline from 2007 to 2015 (APC = –8.0%, 95% CI = –5.3– –10.5) (Fig. 1). We observed an increase in the total number of clients enrolled in drug treatment in Croatia (including clients on methadone, buprenorphine, hospital-based inpatient treatment and therapeutic communities) up to 2012, followed by a slight reduction after that (Fig. 2). The rate of persons enrolled in drug treatment in Croatia increased significantly from 2005 to 2010 (APC = 12.0%, 95% CI = 10.3–13.8), and it remained stable without a significant change from 2010 to 2015 (APC = 0.9%, 95% CI = –0.7–2.5) (Fig. 3). There was a significant increase in the rate of persons on methadone from 2005 to 2015 (APC = 0.9%, 95% CI = 0.2–1.6). The provision of buprenorphine in Croatia grew steeply from its introduction in 2005 to 2008 (APC = 130.4%, 95% CI = 102.1–162.7), and continued with a smaller increase from 2008 until 2015 (APC = 3.6%, 95%

CI = 0.0–7.3), surpassing the rate of clients on methadone in 2012 (Fig. 3). Out of 6,123 persons enrolled in drug treatment in 2015 in Croatia, 41.4% were treated with buprenorphine and 38.7% with methadone. Values used to produce Figs. 1–3 can be found in the Supplementary material Tables 1 to 3.

Discussion

Lifetime prevalence of self-reported drug overdose among PWID in the sample from three Croatian cities was 45.2%, while 4.1% reported overdose in the past 12 months. PWID in our sample who injected more than one type of drug in the past 12 months compared to injecting only heroin, and those enrolled in OAT were more likely to report overdose in the past 12 months. We observed a significant increase in the national OM rates from 2001 to 2007 and a significant decline from 2007 to 2015. The rate of persons enrolled in drug treatment in Croatia increased significantly from 2005 to 2010 and it remained stable without a significant change from 2010 to 2015.

Lifetime prevalence of overdose in our sample (45.2%) was similar to the median of 47% found in a review of global data on non-fatal drug overdose (Martins, Sampson, Cerdá, & Galea, 2015). We observed a lower rate of non-fatal overdose in the past 12 months in our sample (4.1%) compared to the global median rate of 16.8% (Martins et al., 2015). We detected a significant reduction in the OM rates on the national level from 2007 to 2015, which is in line with the observed lower prevalence of non-fatal overdose in the past 12 months in the sample of PWID in three Croatian cities, when compared to global estimates of non-fatal overdose in the past 12 months, and with the observed 11% reduction in the number of high-risk opioid users in Croatia from 2012 to 2015.

Contrary to our expectations, PWID in the sample who were enrolled in OAT were more likely to report overdose in the past 12 months, compared to PWID who were not currently enrolled in OAT. In our sample, 26.6% of PWID reported being enrolled in OAT at the time of the survey, and the national report on persons treated for drug abuse in 2017 reports that, out of all clients enrolled in drug treatment for opioid misuse, 80% reported ever injecting drugs and only 8% reported injecting drugs 30 days prior to participating in the survey (Croatian Institute of Public Health, 2018). Therefore, it is important to note that the majority of participants on OAT do not inject drugs regularly, and the positive association of enrollment in OAT and self-reported overdose refers to the minority of participants enrolled in OAT who continue to inject drugs. While methadone is effective and safe medication for treatment of opioid addiction, there are a number of circumstances that can increase the risk of methadone overdose, such as combining it with multiple drugs (e.g., alcohol, benzodiazepines, cocaine and other substances), which may have a synergistic effect with methadone and cause respiratory and central nervous system depression (EMCDDA, 2009; Sordo et al., 2017). Literature suggests that buprenorphine is less likely to lead to fatal respiratory depression and overdose death compared to methadone as it is a partial opioid agonist (Auriacombe, Franques, & Tignol, 2001). However, the period immediately after leaving the buprenorphine treatment is also associated with the increase in the risk for overdose (Auriacombe et al., 2001; Bell, Butler, Lawrance, Batey, & Salmelainen, 2009; Sordo et al., 2017). The high prevalence of polydrug use and misuse of methadone and buprenorphine that we observed among PWID in our sample could be one of the reasons explaining the positive association of enrolment in OAT and self-reported overdose. The cross-sectional study design does not allow us to infer the causation of this association and further research should explore these assumptions as well as the reasons for high levels of misuse and diversion of OAT medications among PWID in our sample.

Current evidence suggests that OAT reduces all-cause mortality and overdose mortality among PWID and that OAT is an effective method for reducing the harms of opioid addiction (Sordo et al., 2017). However, results of our analysis and current evidence suggest that certain

Table 2

Associations of socio-demographic characteristics, drug use and utilization of harm reduction programmes with the history of self-reported non-fatal overdose in the past 12 months among persons who inject drugs (PWID) in three Croatian cities, 2014–2015 (expressed as unadjusted prevalence ratios [PR] and prevalence ratios adjusted for confounding [aPR] with 95% confidence intervals [CI] and two-sided p-values).

Characteristics	n/N	PR (95% CI)	aPR ^a (95% CI)
Age		p = 0.408	
18-29	7/189	Ref.	–
≥30	27/605	1.52 (0.56-4.15)	
Gender		p = 0.167	
Male	30/630	Ref.	–
Female	4/183	0.47 (0.16-1.37)	
Education		p = 0.800	
Primary school or lower	6/129	Ref.	–
Secondary school or higher	28/693	1.14 (0.41-3.18)	
Monthly income in USD ^b		p = 0.115	
\$0-\$156	19/471	Ref.	–
\$157-\$468	12/198	1.03 (0.47-2.27)	
≥\$469	3/157	0.40 (0.17-1.00)	
Ever incarcerated		p = 0.497	
No	15/399	Ref.	–
Yes	19/426	1.27 (0.64-2.51)	
City of residence		p = 0.054	
Zagreb	14/174	Ref.	–
Rijeka	15/255	0.73 (0.35-1.51)	
Split	5/397	0.16 (0.06-0.43)	
(Split vs Rijeka)	–	0.21 (0.08-0.59)	
Length of injection drug use		p = 0.400	
≤10 years	9/220	Ref.	–
≥11 years	25/606	0.72 (0.33-1.56)	
Drug injected in the past 12 months		p = 0.050	p = 0.050
Only methadone or buprenorphine	8/173	Ref.	Ref.
Only heroin	2/144	0.30 (0.06-1.43)	0.35 (0.06-1.86)
Polydrug use ^c	24/448	1.36 (0.63-2.94)	1.57 (0.74-3.37)
Polydrug vs. only heroin	–	4.52 (1.55-13.18)	4.56 (1.35-15.38)
Currently enrolled in opioid agonist treatment		p = 0.014	p = 0.047
No	15/606	Ref.	Ref.
Yes	19/220	2.30 (1.81-4.49)	1.94 (1.01-3.74)
NSEP ^d was the main source of needles and syringes in the past month		p = 0.468	
No	17/290	Ref.	–
Yes	14/471	1.48 (0.51-4.29)	–

For bivariable and multivariable analysis we used generalized estimating equations (GEE) and modified Poisson regression with a robust standard error, clustered for recruitment chain, with social network size and city of residence as fixed effects in every model to account for respondent-driven sampling (RDS) recruitment method and multisite nature of data collection.

^a The final multivariable model adjusted for confounding for current enrolment in opioid agonist treatment and types of drugs injected in the past 12 months; N (final model) = 759 (71 missing values).

^b United States Dollars. \$1 USD = 6.41 HRK (Croatian national currency *Kuna*) – based on the average exchange rate for the period of the survey duration (November 2014-February 2015).

^c Polydrug use was defined as reporting injecting any two different types of drugs in the past 12 months.

^d Needles and syringe exchange programme.

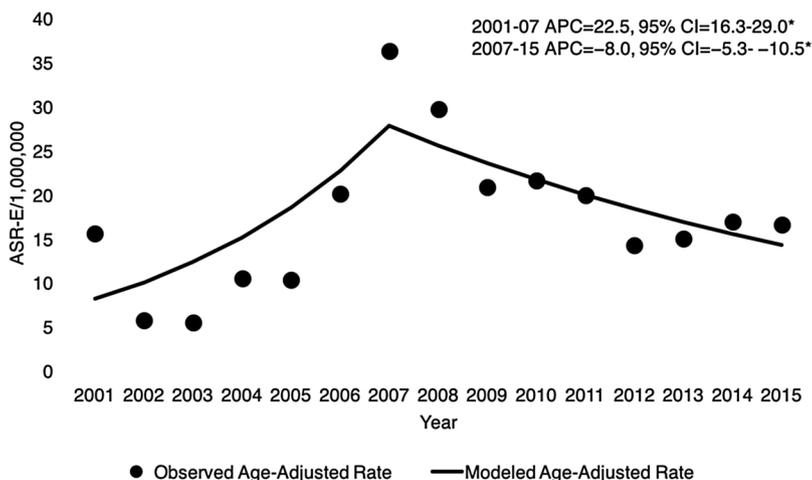


Fig. 1. Rates of overdose-related mortality^a in Croatia, joinpoint trend analysis of truncated age-standardized rates per million population, 2001-2015.

Abbreviations: ASR-E - age-standardized opioid overdose mortality rate adjusted for European population; APC-annual percentage change.

*APC is significantly different from zero at $p < 0.05$.

Trend analysis was done with Surveillance Epidemiology and End Results (SEER) Joinpoint Software, version 4.5.0.1.

^aIncludes three causes of deaths classified as opioid overdose according to the 10th edition of the International Statistical Classification of Diseases and Related Health Problems (ICD-10): X42 - Accidental poisoning by and exposure to narcotics and psychodysleptics [hallucinogens] including: cannabis (derivatives), cocaine, codeine, heroin, lysergide [LSD], mescaline, methadone, morphine, opium (alkaloids). [List of substances applies for X62 and Y12]; X62- Intentional self-poisoning by and exposure to narcotics and psychodysleptics [hallucinogens]; and Y12- External causes of morbidity and mortality: Poisoning by and exposure to narcotics and psychodysleptics [hallucinogens].

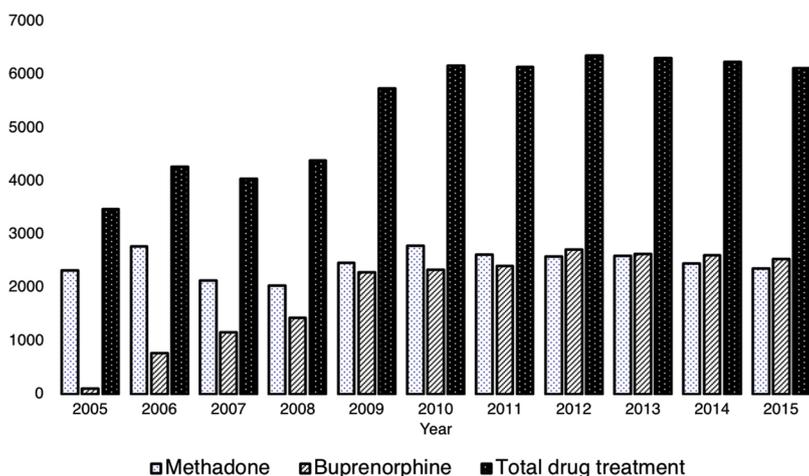


Fig. 2. Number of persons on methadone or buprenorphine treatment and total number of persons enrolled in any type of drug treatment in Croatia, 2005–2015.

*Total number of persons enrolled in any type of drug treatment including clients on methadone or buprenorphine and other means of treatment of drug use disorders such as hospital-based inpatient treatment and therapeutic communities.

precautions should be taken during and after OAT enrollment to increase safety and reduce risk for overdose (EMCDDA, 2017b; Sordo et al., 2017). For example, programmes that allow take-home use of OAT and its (partly) unsupervised use, which is a common practice in Croatia, should inform clients of the risks of using other drugs or medications (Centre for Substance Abuse Treatment, 2009). World Health Organization (WHO) recommends that OAT should be initiated with supervised dosing, followed by assessing response to treatment, and later on allowing unsupervised doses to patients who demonstrate stability (WHO, 2009). Unsupervised administration of methadone can lead to a higher coverage of OAT and has, therefore, public health benefits. However, it can also result in the diversion of methadone and overdose in persons for whom the drug is not prescribed (Shields, Hunsaker, Corey, Ward, & Stewart, 2007). All of these factors should be considered when prescribing OAT to clients.

The higher prevalence of overdose among PWID in our sample who injected more than one type of drugs in the past 12 months was consistent with our assumptions prior to the analysis and with the findings from other studies that identified polydrug use to be associated with a higher risk of non-fatal and fatal overdose among PWID (Gjersing et al., 2013; Nambiar, Agius, Stooze, Hickman, & Dietze, 2015). The majority of PWID in our sample (54.4%) reported using more than one type of drugs in the past 12 months. Additionally, they reported frequent use of alcohol and benzodiazepines in combination with heroin during their last overdose, which both increase the risk of heroin-related overdose due to a reduced capacity to judge the amount of opioids consumed and act synergistically with opioids in depressing respiratory functions

(Coffin et al., 2007; McCance-Katz, Sullivan, & Nallani, 2010).

The observed significant decline in the national OM rates from 2007 to 2015 started shortly after the beginning of the steep increase in the number of clients on buprenorphine, a partial opioid agonist with a lower risk for overdose compared to methadone, that lasted from 2005 to 2008. Additionally, a steady increase in total number of persons on drug treatment started in 2005 and it lasted until 2015. Although the current evidence suggests that enrollment in OAT reduces the risk of overdose mortality (Sordo et al., 2017), and a substantial scale up of OAT in Croatia was followed up by the significant decrease in the national OM rates, we cannot draw causal conclusions from this analysis. It is essential to continue monitoring OM rates and provision of OAT to better understand the reasons of the decrease of OM in Croatia, especially in the light of the increasing trends of OM in Europe and globally. We acknowledge that other conditions such as better awareness of the risk of overdose among PWID, potential under-reporting of deaths related to drug overdose and a decrease in the number of high-risk opioid users all may have contributed to the decline of OM in Croatia.

The first set of interventions to prevent overdose-related harms should include raising awareness and provision of information about conditions associated with increased risk of overdose such as polydrug use or misuse of OAT, screening for risk of overdose to early identify high-risk individuals and provision of high-quality OAT (Darke et al., 2011; Evans et al., 2015; Pierce et al., 2016). Safety of patients on OAT can be increased by education of medical personnel on the appropriate administration of treatment, monitoring patients' health while on treatment, assessing each patient for the use of other drugs and

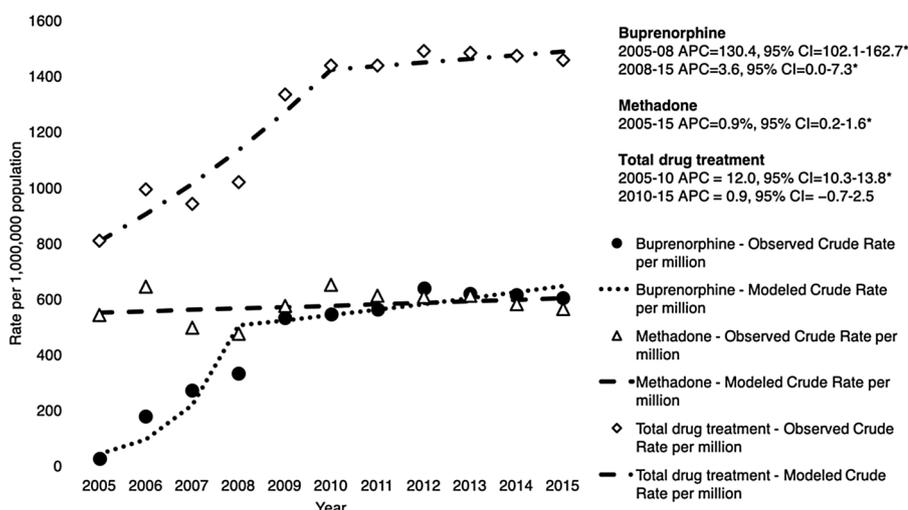


Fig. 3. Methadone, buprenorphine and total drug treatment uptake rates in Croatia, joinpoint trend analysis of crude rates per million population, 2005–2015.

Abbreviations: APC=annual percentage change.

*APC is significantly different from zero at $p < 0.05$. Trend analysis was done with Surveillance Epidemiology and End Results (SEER) Joinpoint Software, version 4.5.0.1.

Total drug treatment includes methadone or buprenorphine and other means of treatment of drug use disorders such as hospital-based inpatient treatment and therapeutic communities.

medications, and setting up appropriate procedures for take-home OAT. Buprenorphine and methadone seem to be equally effective in the maintenance treatment of opioid dependence, but methadone is superior to buprenorphine in retaining persons in treatment while buprenorphine has a lower risk of overdose (Nielsen et al., 2016). These factors should be considered when planning OAT treatment for clients with higher risk of overdose.

The second set of interventions for reducing fatal outcomes of overdoses should focus on providing access to naloxone to persons who are likely to witness an opioid overdose, including persons who inject opioids and other drugs (68% of PWID in our sample witnessed an overdose in their lifetime), their family and friends, and setting up safe injection facilities where individuals can inject pre-obtained drugs under the supervision of healthcare professionals (Doe-Simkins et al., 2014; Semaan et al., 2011). Distribution of take-home naloxone to those likely to witness overdoses (family members, partners, outreach workers, police) and in settings frequented by PWID enables the timely treatment of overdose where emergency help is unavailable or unlikely to reach the overdosing person in time (Giglio, Li, & DiMaggio, 2015; McDonald & Strang, 2016; WHO, 2014).

We acknowledge several limitations in our study. We decided not to use RDS weighted estimates in this analysis, and therefore our findings are specific for the recruited sample and generalization to the entire population of PWID in the included cities should be made with caution. We recruited participants from three largest cities in Croatia, but we cannot generalize our findings to PWID from other parts of Croatia. Research design was cross-sectional and therefore we cannot infer causality for the observed associations. We relied on self-reported data on overdose experiences and we cannot establish the extent of over- or under-reporting of overdose and verify the types of drugs respondents overdosed on. However, overdose is a serious and infrequent condition, which could limit the risk of recall bias, particularly if the timeframe is set to the previous 12 months. Social desirability might have influenced reporting of other drug-related behaviours. It is challenging to estimate the quality of mortality data particularly in the context of declines in a number of autopsies in Croatia, which could have led to under-reporting of OM (Coric & Miler Knezevic, 2016).

Despite listed limitations, our data provide a compelling view of the extent and factors associated with a self-reported drug overdose in the sample of PWID from three largest Croatian cities. Education of PWID about risks of overdose, prevention of misuse and diversion of methadone and buprenorphine and provision of naloxone to PWID and their family and friends, are keys to reducing harm from overdose among PWID in Croatia.

Conflict of interest

We wish to confirm that there are no known conflicts of interest associated with publication “Overdose mortality rates in Croatia and factors associated with self-reported drug overdose among persons who inject drugs in three Croatian cities” and there has been no significant financial support for this work that could have influenced its outcome.

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Informed consent

Informed consent was obtained from all individual participants included in the study.

Contributions

All authors participated in the planning and conception of the research questions and the study design. IB, SH, JB conceptualized the study design and coordinated the study implementation. SH and MS were responsible for analyzing the data. SH, IB and GR drafted the article, and all authors participated in interpreting the data and critically revising the manuscript. All authors read and approved the revised manuscript.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:<https://doi.org/10.1016/j.drugpo.2018.11.017>.

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