Published in final edited form as:

Eur J Epidemiol. 2018 July ; 33(7): 679–688. doi:10.1007/s10654-017-0342-z.

A cross-national analysis of the association between years of implementation of opioid substitution treatments and drug-related deaths in Europe from 1995 to 2013

Phillip L. Marotta^{1,2} and Charlotte A. McCullagh^{1,2}

¹School of Social Work, New York, NY, USA

²Columbia University, New York, NY, USA

Abstract

Data at the individual-level provide evidence that opioid substitution treatment (OST) programs protect against mortality for opioid dependent populations. Prior research has not examined the merits of national implementation of opioid substitution programs for reducing mortality at the country-level. This study elucidates longitudinal associations between country-level implementation of opioid substitution treatment programs on mortality rates of drug related deaths (DRD) from 1995 to 2013 in 30 European nations. Cases of DRD were measured using National Definitions for each country from official sources of data. Preliminary analysis of dispersion of cases of DRD using means and variances justified use of the negative binomial regression model with a population offset. Year and country-level fixed effects negative binomial regression models investigated the association between years of implementation of methadone maintenance therapy (MMT), OST in prison, and high dose buprenorphine treatment (HDBT) implementation and mortality rates from drug related deaths after adjusting for unemployment rates, heroin seizures and per capita expenditures on health. Beta coefficients were converted to Incidence Rate Ratios (IRR) and standard errors bootstrapped using non-parametric methods to adjust for bias (SD_{bs}). The mean mortality rate of DRD was 1.81 from 1995 to 2013. In adjusted models, each additional year of MMT ($IRR = .61$, $SD = .04$, $p < .001$; $SD_{bs} = .08$, $p < .001$), prison OST ($IRR = .90$, $SD = .01$, $p < .001$; $SD_{bs} = .02$, $p < .001$), and HDBT ($IRR = .09$, $SD = .02$, $p < .001$; $SD_{bs} = .02$, $p < .01$) was significantly associated with lower rates of DRDs after adjusting for country and year fixed effects. Implementation of OST programs in the general population and in prison settings may have protected against mortality from drug use at the country-level in Europe from 1995 to 2013.

Keywords

Heroin; Opioid substitution treatment; Overdose

Correspondence to: Phillip L. Marotta.

Conflict of interest All the authors declare that they have no conflict of interest.

Introduction

Drug-related deaths are a major public health problem in the European Union (EU) member states [1]. In 2014, approximately 6800 mortalities were attributed to drug use amounting to an overdose rate of 18.1 per million and opioid misuse is involved in 82% of drug-related deaths in Europe [2, 3]. In the first decade of the twenty-first century, illicit drug use claimed approximately 70,000 lives therefore mortality among people who use drugs remains a critical priority for public health policy for EU member states [2]. The recent rise in popularity of synthetic opioids including fentanyl and its derivatives has contributed to increasing rates of drug related deaths in many EU member states [4, 5]. Over the past several decades, observational studies provide consistent evidence that drug-related deaths are a leading cause of mortality among people who inject drugs (PWID) and populations who misuse opioid analgesic medications [5–11].

The historical progression of mortality rates of DRD in Europe is characterized by a rapid increase in rates between 1990 and 2000 precipitating nations to adopt drug treatment policies that treated drug misuse as a serious and chronic medical problem. Many nations adopted advisory councils on misuse of drugs and surveillance indicators were devised to monitor trends in DRDs [12]. Although overall rates of DRD have declined in Europe, there is considerable variation in trends of mortality rates of DRD in countries throughout Europe that is fueled by heroin use, misuse of prescription opioid analgesic medications and synthetic opioids [13–15]. Some countries including Spain, France and Portugal have experienced a decline in mortality rates of DRDs. Other nations including Estonia, Latvia and Sweden have endured persistently high rates of DRDs.

An empirical study of several European countries estimated 22.8 million patients use prescription opioid analgesic medications of which nearly half a million (455,000) are dependent [16]. In Germany the prevalence of dependence on prescription drugs accounts for 1.6% of the total population or between 1.3 and 1.4 million people [17]. In addition to prescription opioid analgesic and synthetic opioid misuse, variation in implementation of opioid substitution treatments (OST) may explain differences in national mortality rates of DRDs in countries throughout Europe [18]. OST programs are comprehensive interventions consisting of long-term prescribing of opioid medications that function as an alternative to the opioid on which the patient was dependent [19, 20].

Methadone maintenance therapy (MMT) and high-dose buprenorphine treatment (HDBT) are two popular OSTs that were adopted by many countries in Europe during the 1990's and early 2000's to curb rising rates of DRDs due to problem opioid use [21]. Decades of studies support the success of MMT in reducing mortality, improving quality of life and other promising substance misuse outcomes among PWID and populations with OAD [22–31]. For instance, implementation of MMT in Spain is credited with a subsequent reduction in DRDs among people with problem opioid use [22, 32]. Similar research conducted by Torrens et al. [32] found utilization of MMT reduced mortality and decreased substance misuse over a 15-year follow-up period among a sample of patients in Israel. In addition to opioids, Kerr et al. [33] found utilization of MMT was protective against non-fatal overdose for polysubstance users of heroin, cocaine, and benzodiazepines.

High-dose buprenorphine treatment (HDBT), a partial mu-receptor agonist, provides an appealing alternative to MMT because of significantly less risk of fatality from respiratory depression even at high doses and can be administered without direct observation of dosing [34–39]. HDBT was first registered in France in 1996 and, by 2000, 8 EU member states had followed suit [40]. Studies in Europe have found that HDBT decreases deleterious substance abuse outcomes including relapse, overdose mortality, and other morbidities [21, 37, 41]. HDBT offers several advantages over MMT including a lower threshold for fatal respiratory depression thus reducing the likelihood of drug related deaths [21]. Moreover, empirical studies in Europe and other parts of the world suggest very low mortality rates associated with buprenorphine use when taken with a prescription and under supervision of a physician [6].

Widespread data at the individual level throughout Europe and other parts of the world suggest that implementation of OST programs lower mortality rates among populations with problem opioid use [30]. Studies have found attenuated risk of death among opioid dependent populations who are retained in treatment longer compared opioid dependent populations who are not retained treatment [6, 36, 41]. Moreover, patients who leave treatment are 3–4 times as likely to experience drug-related fatalities compared to patients with opioid dependence that are retained in treatment [42, 43].

An abundance of empirical evidence suggests that the criminalization of drug use heightens risk of mortality among people with problem opioid use by virtue of interrupting access to OST programs and increases attrition during periods of incarceration [44, 45]. Populations with problem opioid use are disproportionately represented in prison settings and those who are not provided access to OST interventions while in prison are at an increased likelihood of recidivism, mortality, and other poor outcomes [46, 47, 48, 49]. In response to these harms, many EU member states implemented OST programs in prisons to minimize lapses in treatment and increase retention in care. There is a growing body of experimental and observational studies suggesting that provision of MMT and HDBT in prison reduces mortality rates of DRD among prisoners following release from incarceration [46, 50–56]. Degenhardt et al. [8] found that OST in prison is highly protective in reducing mortality from opioid drug use following release in a retrospective study covering a period of 22 years.

Studies have not looked at relationships between MMT, OST in prison, HDBT and mortality rates of DRD from a cross-national perspective. Analysis of surveillance data of DRD and OST implementation is critical for evaluating the merits of harm minimization strategies and evaluating the impact of interventions in EU member states [10]. Additionally, the implementation of OST programs throughout Europe and other parts of the world are inhibited by prejudices and moral judgments that obscure scientific evidence [32, 57].

Other social structural factors including poverty, unemployment and drug availability may increase rates of overdose [58–62]. Increased availability of heroin including the spread of drug markets and drug trafficking routes are linked to the emergence of injection drug use, overdose and HIV in extant empirical literature [61, 63]. In addition to licit and illicit economic conditions, government spending on health and social protections as a proportion

of gross domestic product has protective effects on the emergence and persistence of negative health outcomes over time [64–67]. Countries that enhance health care systems by investing government funding are more equipped to treat substance abuse problems and prevent overdose than countries that invest less money [64, 65, 67]. Despite growing rates of overdose in many countries, few studies examine the influence of social and structural factors, health systems, harm-reduction implementation on rates of overdose. Scientific research at the cross-national level is crucial to performing objective assessments of the health and social benefits provided by implementing harm reduction interventions that reduce mortality among opioid dependent populations in Europe. To investigate the relative benefits of MMT and HDBT, we undertook a cross-national analysis of data from 30 Member EU states. This study hypothesizes that implementation of methadone maintenance therapy (MMT), MMT in prisons, and high-dose buprenorphine treatment (HDBT) will be associated with lower rates of overdose compared to countries with fewer years of implementation. For control covariates, hypotheses included higher unemployment rates, lower expenditures on health, and greater rates of heroin seizures will be associated with rates of drug related death (DRD) after adjusting for year and country-level fixed effects.

Methods

Data and measures

The European Monitoring Center for Drugs and Drug Addiction (EMCDDA) compiles information on drug use and harm reduction program implementation for EU member states. Years of introduction of substitution treatment with methadone (MMT), OST in prisons and high-dosage buprenorphine treatment (HDBT) were obtained from the EMCDDA. The total number of years of implementation was calculated by subtracting the year of introduction from 2013 for MMT, Prison OST and HDBT. The years of implementation were calculated from the year 2013 dating back to 1995 (if treatment started in 1995 then the value of years of implementation is zero and 18 at 2013).

Drug-related deaths

Data measuring drug-related deaths (DRD) is recorded through member states' Special Registries (Forensic or Police) or General Mortality Registries and reported to EMCDDA annually [68]. This study uses the National Definition method of reporting DRD that records drug related deaths from official sources of data [69].

Control covariates

Annual quantities of heroin seized (kg) from 1995 to 2013 were obtained from the EMCDDA. National data collection and reporting procedures for each of the member states is outlined in the EMCDDA information on methods and definitions [68]. Data on per capita expenditures on health and the unemployment rates for each of the EU member states were obtained through the World Bank [70]. Health expenditures were divided by 1000 to facilitate ease of interpretation. The number of drug-related deaths and heroin seizures for each country were converted to rates per 100,000 using total population estimates from the World Bank for descriptive analyses and population estimates were used as offsets for

regression analyses. The final dataset included 30 countries with a total of 493 observations from 1995 to 2013.

Statistical analyses

Descriptive statistics and means were calculated for each country and overall incidence rates of DRDs were visualized for the entire sample of 30 countries from 1995 to 2011. Year and country-level fixed effects models estimated relationships between years of substitution treatment implementation and DRDs after adjusting for expenditures on health and unemployment. By introducing country and time dummy variables, fixed-effects models controlled for the effects of observable or unobservable time and country-level invariant characteristics [71–73]. Fixed-effects models minimized potential omitted variable bias introduced by unmeasured within country effects by modeling only the net effects of time-variant predictor variables [71].

Given that the dependent variables in this study are counts of DRDs, model selection must take into account non-normal distribution and overdispersion of the data [74, 75]. A variance that is greater than the mean, warrants selection of the negative binomial regression to accommodate overdispersion of the data [75–77]. To select the most appropriate model, a descriptive analysis comparing the mean of counts were compared against the variance for DRDs [76].

Preliminary data analyses involved visual inspection of the data for outliers with primary independent variables using box plot graphs (available on request). Visual inspection revealed that Sweden, Denmark the Netherlands and the UK were outliers on years of MMT implementation with greater than 40 years of prior implementation. Non-parametric bootstrapping techniques were employed to correct for potential effects of outliers introduced by countries that implemented OAT for much longer than other countries. Non-parametric bootstrapping uses the distribution of the sample to conduct a series of replications without replacement to generate many estimates of standard errors that are used to approximate a bias-corrected standard error of a parameter coefficient included in the adjusted models [78]. Bootstrapping is shown to correct bias in the fixed effects maximum likelihood estimator in non-linear panel data that is inconsistent when the time T is short and fixed [74, 77]. Prior literature suggests asymptotic validity of bootstrap bias corrections for the model parameters in unconditional fixed effects models [77].

Table 1 presents means and variances for each of the count measures of drug-related deaths. The variance was greater than the mean by a factor of 734.86. Based upon exploratory analyses of means and variances for counts of drug-related deaths, the fixed-effects negative binomial regression approach was selected for models adjusting for year and country-specific effects.

Results

Descriptive analyses

Descriptive statistics and means for each country and the overall sample are provided in Table 2. The total number of countries reporting data on DRDs was 30. Cyprus did not

provide data on year of MMT and Prison OST introduction and Turkey did not report any data on substitution treatment. Greece and Slovakia did not implement prison OST and Bulgaria, Hungary and Poland did not implement HDBT during the study period. From 1995 to 2013, the mean incidence rates of drug-related deaths was 1.18 per 100,000 of the population. Over the same period, the mean quantity of heroin seized was 1.84 kg per 100,000 of the population, the mean per capita expenditures on health was 2118.59 and the average unemployment rate was 6.78%.

Longitudinal patterns in the overall incidence rate of drug-related deaths (per 100,000) are provided in Fig. 1. Rates of DRD peaked from 1999 to 2000 and subsequently underwent a decline until 2003 when rates began to increase.

Negative binomial regressions

Fixed effects negative binomial regression models estimated unadjusted relationships between years of MMT, prison OST, and HDBT substitution treatment implementation and logged rates of drug-related deaths and then adjusted for heroin seizures, expenditures on health and unemployment rates. Incidence Rate Ratios (IRR) are reported in all adjusted and unadjusted models.

Methadone maintenance therapy (MMT)

Table 3 presents fixed effects negative binomial regression models assessing the association between years of MMT implementation on counts of drug-related overdose with a population offset. The models included a total of 30 countries for National Definition drug-related deaths. In the unadjusted model, years of MMT implementation was negatively associated with incidence rates of National Definition DRDs (IRR = .64 SD = .04, $p < .001$). In the adjusted models with bootstrapped standard errors, years of MMT were associated with significantly lower National Definition DRDs (IRR = .61, SD = .04, $p < .001$; $SD_{bs} = .08$, $p < .001$). Unemployment was associated with lower National Definition drug-related deaths (IRR = .98, SD = .006, $p < .01$; $SD_{bs} = .009$, $p < .05$). The number of observations in the adjusted models was 431 for National Definition drug-related deaths.

Prison based opioid substitution programs

Table 4 provides year-and country-level fixed-effects negative binomial models assessing the association between years of prison OST on counts of drug-related overdose with a population offset from 1995 to 2013 for 22 countries. In the unadjusted models, years of prison OST implementation predicted significantly lower National Definition DRDs (IRR = .93, SD = .009, $p < .001$). These relationships persisted in the adjusted models and prison OST predicted lower rates National Definition DRDs (IRR = .90, SD = .01, $p < .001$; $SD_{bs} = .02$, $SD_{bs} = .02$, $p < .001$) after adjusting for heroin seizures, health expenditures, and unemployment. In the adjusted models, the total number of observations was 332 for National Definition DRDs.

High dose buprenorphine therapy (HDBT)

Table 5 provides year and country-specific fixed effects negative binomial regression models assessing the association between HDBT and counts of drug-related deaths with a

population offset for 26 countries. In the unadjusted models, years of HDBT implementation were associated with fewer National Definition DRDs (IRR = .91, SD = .01, $p < .001$). In the adjusted models with a total of 400 observations, years of HDBT were associated with fewer National Definition DRDs (IRR = .92, SD = .02, $p < .001$; $SD_{bs} = p < .01$). Unemployment was associated with fewer National Definition DRDs (IRR = .98, SD = .008, $p < .01$; $SD_{bs} = .01$, $p < .01$).

Discussion

The central aim of this longitudinal exploratory study was to elucidate the association between OST implementation and mortality rates of DRDs in Europe. Findings identified a statistically significant inverse relationship between years of MMT, Prison OST, and HDBT implementation and drug-related deaths after adjusting for year and country-level fixed effects, heroin seizures, expenditures on health and unemployment. These findings remained significant after bootstrapping our standard error estimates using nonparametric methods. Our findings align with existing literature at the individual-level suggesting early implementation of OST programs may have lower mortality rates of DRDs than countries that hesitated in their response to problem opioid use.

Several important implications are identified by this study for health policy in Europe, clinical care of people with opioid dependence and research. Years of implementation of OST may translate into direct public health benefits for EU nations with rapidly expanding opioid dependence problems. This is a critical lesson for countries that are immersed in burgeoning rates of heroin, prescription opioid and synthetic opioid misuse throughout Europe. The nature of opioid dependency is evolving rapidly in Europe and is characterized by a shift from dependency on predominantly heroin to now include prescription and synthetic opioids [4, 76].

Second, implementing OST in prison settings is highly protective against mortality rates from DRD and may assist in ensuring that the gains achieved by community-based OST programs are sustained within correctional settings. There is mounting empirical evidence suggesting that interventions to reduce the supply of illegal drugs or diversion of prescription opioids through criminalizing drug use has imposed deleterious public health consequences on populations that are dependent on opioids by virtue of heightened mortality rates of DRD, relapse and increased recidivism [79–81]. In addition to DRD, studies suggest that prisons create social conditions that are conducive to rapidly unfolding rates of infectious diseases including HIV, HCV, and Tuberculosis [82]. Findings from this study support existing empirical inquiry calling into question national drug response strategies that prioritize supply reduction interventions involving criminalization over public health interventions embracing demand-reduction through a medical model of substance abuse treatment [79].

Third, protective relationships between unemployment rates and overdose is surprising given that the abundance of existing literature on the individual level showing a positive relationship between higher rates of poverty and overdose [59–62]. At the national level, wealthier nations may have greater rates of overdose due to internal factors of high rates of

inequality and poor access to health among the poor compared to poorer nations with less inequality in the distribution of economic and health resources [83, 84]. The deleterious consequences of problem opioid use may be influenced less by the resources at the disposal of wealthier nations but rather how countries decide to engage in social responses to drug use by virtue of implementation of OST programs and other interventions. Countries with higher rates of unemployment and poverty may also lack adequate infrastructure to conduct autopsies on deaths with suspected causes related to drug use thereby underreporting overdose rates. In both of these contexts, one could expect to see a negative association between higher rates of unemployment and lower rates of overdose.

Findings from this empirical study open a new line of inquiry into substance abuse research and provide a compelling justification for additional cross-national research into the impact of OST implementation on public health outcomes at the national level. Nonetheless, there are several limitations of this study that give rise to fruitful avenues of future research. This study aimed to examine the impact of OST program implementation on mortality rates longitudinally and therefore was limited to variables with data collected over a sufficient window of time. Currently, socioeconomic, demographic, and health variables are collected in Europe with timespans that will eventually become feasible to perform longitudinal analyses. Future comparative social policy analyses could include other indicators including doses of methadone maintenance per patient, national harm reduction coverage and uptake of OST. Improvements are needed in measurement that standardize how DRD is measured in Europe. Presently the EMCDDA emphasizes that researchers take some degree of caution in analyzing DRD in Europe due to variation in how deaths are recorded across countries.

It is possible that other structural factors may play a role in rates of overdose rather than years of implementation. Policies and practices at the national level stigmatizing and discriminating against people who use drugs may prevent people who use drugs from accessing substance abuse treatment, and increase rates of overdose [61, 63]. For instance, research suggests that punitive and aggressive police practices around methadone maintenance facilities may interfere with linkage and retention in substance abuse treatment and harm reduction programs [85, 86]. Nations with high rates of stigma and discrimination by police toward people who inject drugs may increase rates of unsafe injection practices including rushing injections and improperly preparing drug solutions increasing risk of overdose. Future research is necessary exploring the impact of other structural factors including the legal system and policies, health care and societal stigma.

Given the exploratory nature of this study, we did not examine the effects of combination interventions for attenuating rates of DRD in Europe. Studies suggest that the availability of multiple types of OST interventions for opioid dependence is most promising in improving the health and social welfare of populations that are dependent on opioids. This study did not account for variation in treatment and policy factors related to implementation of MMT, OST in Prison, and HDBT programs including dosing practices, harm reduction policies and number of clinics. Some countries waited several years after the opening of the first clinic to implement nationwide harm reduction implementation policies. There is substantial variation and nuance in how countries embraced policies of harm reduction that are not captured by measuring the main determinants as years of implementation. Findings from this

study call for future research incorporating treatment and policy factors related to implementation of substance use and overdose prevention in Europe.

Some of the effects observed in fixed effects models may be impacted by the factors that influence the heroin epidemic outside of the time-period of this analysis. For numerous EU countries that were part of the former Warchau Pact, the treatment response started after 1989 compared to Western Europe where the epidemic emerged in the 1970's [87]. The period of methadone treatment may be related to political changes in Europe resulting from dissolution of the Warchau Pact. It is not possible to assess this potential confounding or other factors that are outside the time period of analysis in this study. Future cross-national research with more historical data on treatment and overdose could illuminate information on other potential confounders.

This study examined implementation of HDBT and MMT and OST in Prisons for opioid dependence in Europe but we did not include other OST programs that are gaining traction in Europe. Future research would benefit from exploring how interventions such as heroin assisted treatment, slow-release morphine and safe injection facilities influence mortality from opioid use at the national level. Also, longitudinal data was not available on naloxone implementation or population responses to overdose. Mounting empirical studies suggest that the availability of naloxone, bystander responses and law enforcement training are crucial interventions to reduce overdose mortality from opioids [88, 89, 90, 91]. Additional research at the national level is necessary to elucidate how naloxone and the responses of community members and law enforcement officers influence mortality rates from drug use.

Conclusion

This study reinforces extant literature highlighting the immense health benefits provided by OST programs in Europe and other parts of the world. Given the absence of cross-national investigations into drivers of mortality rates due to DRD, this study provides a new approach to examining the potential public health benefits of harm reduction policies. Implementation of OST programs may improve the basic human rights and health of opioid dependent populations by virtue of reducing mortality rates from problem opioid use in Europe.

Acknowledgments

The following research by Phillip Marotta was supported by a T-32 Training Fellowship by the National Institute on Drug Abuse (T32DA037801).

References

1. Frisher, M., Baldacchino, A., Crome, I., Bloor, R. Preventing opioid overdoses in Europe: A critical assessment of known risk factors and preventative measures. Lisbon: European Monitoring Centre for Drugs and Drug Addiction, EMCDDA; 2012. Technical paper
2. European Monitoring Centre for Drugs and Drug Addiction. [Accessed 10 Jan 2016] European drug report. 2016. <http://www.emcdda.europa.eu/edr2016>
3. European Monitoring Centre for Drugs and Drug Addiction. [Accessed 10 Jan 2016] Preventing overdose deaths in Europe. Retrieved from <http://www.emcdda.europa.eu/topics/pods/preventing-overdose-deaths>

4. EMCDDA European Monitoring Centre for Drugs and Drug Addiction. [Accessed 10 Jan 2016] Fentanyl in Europe EMCDDA trendspotter study. 2012. http://www.emcdda.europa.eu/attachements.cfm/att_191974_EN_TD3112230ENN_Fentanyl.pdf
5. Mounteney J, Giraudon I, Denissov G, Griffiths P. Fentanyls: are we missing the signs? Highly potent and on the rise in Europe. *Int J Drug Policy*. 2015; 26(7):626–31. [PubMed: 25976511]
6. Bell JR, Butler B, Lawrance A, Batey R, Salmelainen P. Comparing overdose mortality associated with methadone and buprenorphine treatment. *Drug Alcohol Depend*. 2009; 104(1):73–7. [PubMed: 19443138]
7. Clausen T, Anchersen K, Waal H. Mortality prior to, during and after opioid maintenance treatment (OMT): a national prospective cross-registry study. *Drug Alcohol Depend*. 2008; 94(1):151–7. [PubMed: 18155364]
8. Degenhardt L, Larney S, Randall D, Burns L, Hall W. Causes of death in a cohort treated for opioid dependence between 1985 and 2005. *Addiction*. 2014; 109(1):90–9. [PubMed: 23961881]
9. Hulse GK, English DR, Milne E, Holman CDJ. The quantification of mortality resulting from the regular use of illicit opiates. *Addiction*. 1999; 94(2):221–9. [PubMed: 10396790]
10. Connock M, Juarez-Garcia A, Jowett S, Frew E, Liu Z, Taylor RJ, Fry-Smith A, Day E, Lintzeris N, Roberts T, Burls A. Methadone and buprenorphine for the management of opioid dependence: a systematic review and economic evaluation. *Health Technol Assess*. 2007; 11:1–171.
11. Espelt A, Barrio G, Álamo-Junquera D, Bravo MJ, Sarasa-Renedo A, Vallejo F, Molist G, Brugal MT. Lethality of opioid overdose in a community cohort of young heroin users. *Eur Addict Res*. 2015; 21(6):300–6. [PubMed: 26022713]
12. Morgan O, Vicente J, Griffiths P, Hickman M. Trends in overdose deaths from drug misuse in Europe: what do the data tell us? *Addiction*. 2008; 103(5):699–700. [PubMed: 18412741]
13. Casati A, Sedefov R, Pfeiffer-Gerschel T. Misuse of medicines in the European Union: a systematic review of the literature. *Eur Addict Res*. 2012; 18(5):228–45. [PubMed: 22572594]
14. Kraus M, Lintzeris N, Maier C, Savage S. Recommendations for the prevention, detection, treatment and management of prescription opioid analgesic dependence: outcomes from the opioid analgesic dependence education nexus (open) meeting. *Int J Ment Health Addict*. 2016; 14(3): 313–21. [PubMed: 27340378]
15. Van Amsterdam J, van den Brink W. The misuse of prescription opioids: a threat for Europe? *Curr Drug Abuse Rev*. 2015; 8(1):3–14. [PubMed: 26084418]
16. Kraus M, Lintzeris N, Maier C, Savage S. Recommendations for the prevention, detection, treatment and management of prescription opioid analgesic dependence: outcomes from the Opioid Analgesic Dependence Education Nexus (OPEN) meeting. *Int J Ment Health Addict*. 2016; 14(3):313–21. [PubMed: 27340378]
17. Glaeske, G. Duetsch Hauptstelle gegen die Suchtgefahren: Jahrbuch Sucht. Geesthach; Neuland: 2005. Psychotrope und andere Arzneimittel mit Missbrauchs- und Abhängigkeitspotential (Psychotrope and other pharmaceuticals with abuse or dependence potential); p. 52–68.
18. European Monitoring Centre for Drugs and Drug Addiction. [Accessed 10 Jan 2016] Health and social responses. <http://www.emcdda.europa.eu/edr2016>
19. Kimber, J., Palmateer, N., Hutchinson, SJ., Hickman, M., Goldberg, DJ., Rhodes, T. Harm reduction among injecting drug users-evidence of effectiveness. Harm reduction: evidence, impacts and challenges EMCDDA; Lisbon. April 2010; European Monitoring Centre for Drugs and Drug Addiction; 2010. p. 115–163.
20. Stevens, A. Drugs, crime and public health: the political economy of drug policy. London: Routledge; 2010.
21. Schwartz RP, Gryczynski J, O'Grady KE, Sharfstein JM, Warren G, Olsen Y, Mitchell SG, Jaffe JH. Opioid agonist treatments and heroin overdose deaths in Baltimore, Maryland, 1995–2009. *Am J Public Health*. 2013; 103(5):917–22. [PubMed: 23488511]
22. Brugal MT, Domingo-Salvany A, Puig R, Barrio G, Garcia de Olalla P, De La Fuente L. Evaluating the impact of methadone maintenance programmes on mortality due to overdose and aids in a cohort of heroin users in Spain. *Addiction*. 2005; 100(7):981–9. [PubMed: 15955014]
23. Caplehorn JR, Dalton MS, Haldar F, Petrenas AM, Nisbet JG. Methadone maintenance and addicts' risk of fatal heroin overdose. *Subst Use Misuse*. 1996; 31(2):177–96. [PubMed: 8834006]

24. Davstad I, Stenbacka M, Leifman A, Romelsjö A. An 18-year follow-up of patients admitted to methadone treatment for the first time. *J Addict Dis.* 2009; 28(1):39–52. [PubMed: 19197594]
25. Degenhardt L, Randall D, Hall W, Law M, Butler T, Burns L. Mortality among clients of a state-wide opioid pharmacotherapy program over 20 years: risk factors and lives saved. *Drug Alcohol Depend.* 2009; 105(1):9–15. [PubMed: 19608355]
26. Fei JTB, Yee A, Habil MHB, Danaee M. Effectiveness of methadone maintenance therapy and improvement in quality of life following a decade of implementation. *J Subst Abuse Treat.* 2016; 69:50–6. [PubMed: 27568510]
27. Langendam MW, Van Brussel GH, Coutinho RA, Van Ameijden EJ. The impact of harm-reduction-based methadone treatment on mortality among heroin users. *Am J Public Health.* 2001; 91(5):774. [PubMed: 11344886]
28. Marshall BD, Milloy MJ, Wood E, Montaner JS, Kerr T. Reduction in overdose mortality after the opening of North America's first medically supervised safer injecting facility: a retrospective population-based study. *Lancet.* 2011; 377(9775):1429–37. [PubMed: 21497898]
29. Mattick RP, Breen C, Kimber J, Davoli M. Methadone maintenance therapy versus no opioid replacement therapy for opioid dependence. *Cochrane Database Syst Rev.* 2009; 3(3):CD002209.
30. Gibson A, Degenhardt L, Mattick RP, Ali R, White J, O'Brien S. Exposure to opioid maintenance treatment reduces long-term mortality. *Addiction.* 2008; 103(3):462–8. [PubMed: 18190664]
31. Peles E, Schreiber S, Adelson M. 15-Year survival and retention of patients in a general hospital-affiliated methadone maintenance treatment (MMT) center in Israel. *Drug Alcohol Depend.* 2010; 107(2):141–8. [PubMed: 19914783]
32. Torrens M, Fonseca F, Castillo C, Domingo-Salvany A. Methadone maintenance treatment in Spain: the success of a harm reduction approach. *Bull World Health Organ.* 2013; 91(2):136–41. [PubMed: 23554526]
33. Kerr T, Fairbairn N, Tyndall M, Marsh D, Li K, Montaner J, Wood E. Predictors of non-fatal overdose among a cohort of polysubstance-using injection drug users. *Drug Alcohol Depend.* 2007; 87(1):39–45. [PubMed: 16959438]
34. Auriacombe M, Franques P, Tignol J. Deaths attributable to methadone vs buprenorphine in France. *JAMA.* 2001; 285(1):45. [PubMed: 11150107]
35. Barnett PG, Rodgers JH, Bloch DA. A meta-analysis comparing buprenorphine to methadone for treatment of opiate dependence. *Addiction.* 2001; 96(5):683–90. [PubMed: 11331027]
36. Johnson RE, Jaffe JH, Fudala PJ. A controlled trial of buprenorphine treatment for opioid dependence. *JAMA.* 1992; 267(20):2750–5. [PubMed: 1578593]
37. Krook AL, Brørs O, Dahlberg J, Grouff K, Magnus P, Røysamb E, Waal H. A placebo-controlled study of high dose buprenorphine in opiate dependents waiting for medication-assisted rehabilitation in Oslo, Norway. *Addiction.* 2002; 97(5):533–42. [PubMed: 12033654]
38. Umbricht A, Huestis MA, Cone EJ, Preston KL. Effects of high-dose intravenous buprenorphine in experienced opioid abusers. *J Clin Psychopharmacol.* 2004; 24(5):479–87. [PubMed: 15349002]
39. Soyka M, Apelt SM, Lieb M, Wittchen HU. One-year mortality rates of patients receiving methadone and buprenorphine maintenance therapy: a nationally representative cohort study in 2694 patients. *J Clin Psychopharmacol.* 2006; 26(6):657–60. [PubMed: 17110826]
40. Fatseas M, Auriacombe M. Why buprenorphine is so successful in treating opiate addiction in France. *Curr Psychiatry Rep.* 2007; 9(5):358–64. [PubMed: 17915074]
41. Kakko J, Svanborg KD, Kreek MJ, Heilig M. 1-year retention and social function after buprenorphine-assisted relapse prevention treatment for heroin dependence in Sweden: a randomised, placebo- controlled trial. *Lancet.* 2003; 361(9358):662–8. [PubMed: 12606177]
42. Davoli M, Bargagli AM, Perucci CA, Schifano P, Belleudi V, Hickman M, Salamina G, Diecidue R, Vigna-Taglianti F, Faggiano F. Risk of fatal overdose during and after specialist drug treatment: the VEdette study, a national multi-site prospective cohort study. *Addiction.* 2007; 102(12):1954–9. [PubMed: 18031430]
43. Zanis DA, Woody GE. One-year mortality rates following methadone treatment discharge. *Drug Alcohol Depend.* 1998; 52(3):257–60. [PubMed: 9839152]
44. Butler T, Kariminia A, Levy M, Murphy M. The self-reported health status of prisoners in New South Wales. *Aust N Z J Public Health.* 2004; 28(4):344–50. [PubMed: 15704699]

45. Nordt C, Stohler R. Combined effects of law enforcement and substitution treatment on heroin mortality. *Drug Alcohol Rev.* 2010; 29(5):540–5. [PubMed: 20887578]
46. Dolan KA, Shearer J, MacDonald M, Mattick RP, Hall W, Wodak AD. A randomised controlled trial of methadone maintenance treatment versus wait list control in an Australian prison system. *Drug Alcohol Depend.* 2003; 72(1):59–65. [PubMed: 14563543]
47. Favrod-Coune T, Baroudi M, Casillas A, Rieder JP, Gétaz L, Barro J, Gaspoz JM, Broers B, Wolff H. Opioid substitution treatment in pretrial prison detention: a case study from Geneva, Switzerland. *Swiss Med Wkly.* 2013; 143:w13898. [PubMed: 24186493]
48. Springer SA, Chen S, Altice FL. Improved HIV and substance abuse treatment outcomes for released HIV-infected prisoners: the impact of buprenorphine treatment. *J Urb Health.* 2010; 87(4): 592–602.
49. Strang J, Bird SM, Parmar MK. Take-home emergency naloxone to prevent heroin overdose deaths after prison release: rationale and practicalities for the N-ALIVE randomized trial. *J Urb Health.* 2013; 90(5):983–96.
50. Dolan KA, Wodak AD, Hall WD. Methadone maintenance treatment reduces heroin injection in New South Wales prisons. *Drug Alcohol Rev.* 1998; 17(2):153–8. [PubMed: 16203480]
51. Gordon MS, Kinlock TW, Schwartz RP, O'Grady KE. A randomized clinical trial of methadone maintenance for prisoners: findings at 6 months post-release. *Addiction.* 2008; 103(8):1333–42. [PubMed: 18855822]
52. Heimer R, Catania H, Newman RG, Zambrano J, Brunet A, Ortiz AM. Methadone maintenance in prison: evaluation of a pilot program in Puerto Rico. *Drug Alcohol Depend.* 2006; 83(2):122–9. [PubMed: 16332415]
53. Kinlock TW, Gordon MS, Schwartz RP, Fitzgerald TT, O'Grady KE. A randomized clinical trial of methadone maintenance for prisoners: results at 12 months postrelease. *J Subst Abuse Treat.* 2009; 37(3):277–85. [PubMed: 19339140]
54. Kinlock TW, Gordon MS, Schwartz RP, O'Grady KE. A study of methadone maintenance for male prisoners 3-month postrelease outcomes. *Crim Justice Behav.* 2008; 35(1):34–47. [PubMed: 18612373]
55. Kinlock TW, Gordon MS, Schwartz RP, O'Grady K, Fitzgerald TT, Wilson M. A randomized clinical trial of methadone maintenance for prisoners: results at 1-month post-release. *Drug Alcohol Depend.* 2007; 91(2):220–7. [PubMed: 17628351]
56. Magura S, Lee JD, Hershberger J, Joseph H, Marsch L, Shropshire C, Rosenblum A. Buprenorphine and methadone maintenance in jail and post-release: a randomized clinical trial. *Drug Alcohol Depend.* 2009; 99(1):222–30. [PubMed: 18930603]
57. Bevan G. Problem drug use the public health imperative: what some of the literature says. *Subst Abuse Treat Prev Policy.* 2009; 4(1):1. [PubMed: 19196468]
58. Bazazi AR, Zelenev A, Fu JJ, Yee I, Kamarulzaman A, Altice FL. High prevalence of non-fatal overdose among people who inject drugs in Malaysia: correlates of overdose and implications for overdose prevention from a cross-sectional study. *Int J Drug Policy.* 2015; 26(7):675–81. [PubMed: 25532449]
59. Fischer B, Brissette S, Brochu S, Bruneau J, El-Guebaly N, Noël L, Rehm J, Tyndall M, Wild C, Mun P, Haydon E. Determinants of overdose incidents among illicit opioid users in 5 Canadian cities. *Can Med Assoc J.* 2004; 171(3):235–9. [PubMed: 15289420]
60. Green TC, Grau LE, Blinnikova KN, Torban M, Krupitsky E, Ilyuk R, Kozlov A, Heimer R. Social and structural aspects of the overdose risk environment in St. Petersburg, Russia. *Int J Drug Policy.* 2009; 20(3):270–6. [PubMed: 18774283]
61. Rhodes T, Singer M, Bourgois P, Friedman SR, Strathdee SA. The social structural production of HIV risk among injecting drug users. *Soc Sci Med.* 2005; 61(5):1026–44. [PubMed: 15955404]
62. Milloy MJ, Fairbairn N, Hayashi K, Suwannawong P, Kaplan K, Wood E, Kerr T. Overdose experiences among injection drug users in Bangkok, Thailand. *Harm Reduct J.* 2010; 7(1):9. [PubMed: 20465842]
63. Strathdee SA, Hallett TB, Bobrova N, Rhodes T, Booth R, Abdool R, Hankins CA. HIV and risk environment for injecting drug users: the past, present, and future. *Lancet.* 2010; 376(9737):268–84. [PubMed: 20650523]

64. Bokhari FA, Gai Y, Gottret P. Government health expenditures and health outcomes. *Health Econ.* 2007; 16(3):257–73. [PubMed: 17001737]
65. Bradley EH, Elkins BR, Herrin J, Elbel B. Health and social services expenditures: associations with health outcomes. *Qual Saf Health Care.* 2011; 20:826–31.
66. Nixon J, Ulmann P. The relationship between health care expenditure and health outcomes. *Eur J Health Econ.* 2006; 7(1):7–18. [PubMed: 16429295]
67. Marotta PL, McCullagh CA. A cross-national analysis of the effects of methadone maintenance and needle and syringe program implementation on incidence rates of HIV in Europe from 1995 to 2011. *Int J Drug Policy.* 2016; 32:3–10. [PubMed: 27212656]
68. European Monitoring Center for Drugs and Drug Addiction. [Accessed 10 Jan 2016] Methods and definitions. Retrieved from <http://www.emcdda.europa.eu/stats07/DRD/methods>
69. World Health Organization. The ICD-10 classification of mental and behavioural disorders: clinical descriptions and diagnostic guidelines. Geneva: World Health Organization; 1992.
70. World Bank Group. , editor. World development indicators 2012. Washington, DC: World Bank Publications; 2012.
71. Kreft, IG., Kreft, I., de Leeuw, J. Introducing multilevel modeling. Thousand Oaks: Sage; 1998.
72. Rabe-Hesketh, S., Skrondal, A. Multilevel and longitudinal modeling using Stata. College Station: STATA Press; 2008.
73. Snijders, TA. Multilevel analysis. Berlin: Springer; 2011.
74. Hilbe, JM. Negative binomial regression. Cambridge: Cambridge University Press; 2011.
75. Piegorsch WW. Maximum likelihood estimation for the negative binomial dispersion parameter. *Biometrics.* 1990; 46:863–7. [PubMed: 2242417]
76. Gardner W, Mulvey EP, Shaw EC. Regression analyses of counts and rates: Poisson, overdispersed Poisson, and negative binomial models. *Psychol Bull.* 1995; 118(3):392. [PubMed: 7501743]
77. Kim MS, Sun Y. Bootstrap and k-step bootstrap bias corrections for the fixed effects estimator in nonlinear panel data models. *Econom Theory.* 2016; 32(6):1523–68.
78. Cameron, AC., Trivedi, PK. Microeconometrics using stata. Vol. 2. College Station: Stata press; 2010.
79. Greenfield VA, Paoli L. If supply-oriented drug policy is broken, can harm reduction help fix it? Melding disciplines and methods to advance international drug-control policy. *Int J Drug Policy.* 2012; 23(1):6–15. [PubMed: 21689918]
80. Weatherburn D, Jones C, Freeman K, Makkai T. Supply control and harm reduction: lessons from the Australian heroin ‘drought’. *Addiction.* 2003; 98(1):83–91. [PubMed: 12492758]
81. Wood E, Tyndall MW, Spittal PM, Li K, Anis AH, Hogg RS, Montaner JS, O’shaughnessy MV, Schechter MT. Impact of supply-side policies for control of illicit drugs in the face of the AIDS and overdose epidemics: investigation of a massive heroin seizure. *Can Med Assoc J.* 2003; 168(2):165–9. [PubMed: 12538544]
82. Altice FL, Azbel L, Stone J, Brooks-Pollock E, Smyrnov P, Dvoriak S, Taxman FS, El-Bassel N, Martin NK, Booth R, Stöver H. The perfect storm: incarceration and the high-risk environment perpetuating transmission of HIV, hepatitis C virus, and tuberculosis in Eastern Europe and Central Asia. *Lancet.* 2016; 388(10050):1228–48. [PubMed: 27427455]
83. Cerdá M, Ransome Y, Keyes KM, Koenen KC, Tardiff K, Vlahov D, Galea S. Revisiting the role of the urban environment in substance use: the case of analgesic overdose fatalities. *Am J Public Health.* 2013; 103(12):2252–60. [PubMed: 24134362]
84. Nandi A, Galea S, Ahern J, Bucciarelli A, Vlahov D, Tardiff K. What explains the association between neighborhood-level income inequality and the risk of fatal overdose in New York City? *Soc Sci Med.* 2006; 63(3):662–74. [PubMed: 16597478]
85. Beletsky L, Grau LE, White E, Bowman S, Heimer R. The roles of law, client race and program visibility in shaping police interference with the operation of US syringe exchange programs. *Addiction.* 2011; 106(2):357–65. [PubMed: 21054615]
86. Davis CS, Burris S, Kraut-Becher J, Lynch KG, Metzger D. Effects of an intensive street-level police intervention on syringe exchange program use in Philadelphia PA. *Am J Public Health.* 2005; 95(2):233–6. [PubMed: 15671455]

87. Gyarmathy VA, Neaigus A. Marginalized and socially integrated groups of IDUs in Hungary: potential bridges of HIV infection. *J Urb Health*. 2005; 82(4):iv101–12.
88. Clark AK, Wilder CM, Winstanley EL. A systematic review of community opioid overdose prevention and naloxone distribution programs. *J Addict Med*. 2014; 8(3):153–63. [PubMed: 24874759]
89. Walley AY, Doe-Simkins M, Quinn E, Pierce C, Xuan Z, Ozonoff A. Opioid overdose prevention with intranasal naloxone among people who take methadone. *J Subst Abuse Treat*. 2013; 44(2): 241–7. [PubMed: 22980450]
90. Davis CS, Carr D, Southwell JK, Beletsky L. Engaging law enforcement in overdose reversal initiatives: authorization and liability for naloxone administration. *Am J Public Health*. 2015; 105(8):1530–7. [PubMed: 26066921]
91. Strathdee SA, Beletsky L, Kerr T. HIV, drugs and the legal environment. *Int J Drug Policy*. 2015; 26:S27–32. [PubMed: 25265900]

Fig. 1.
Drug-related deaths in 30 European Countries

Table 1
Descriptive statistics for 30 nations for years of harm reduction implementation 1995–2013

Country	Years of OST implementation				Control variables mean (SD)		
	DRDs	MMT	OST prison	HDBT	Heroin seizures	Expenditures on health	Unemp. rate
Austria	2.05 (.34)	26	26	15	1.59 (1.02)	3509.67 (876.62)	4.25 (.48)
Belgium	1.02 (1.02)	19	9	10	2.08 (2.44)	3007.40 (945.90)	8.05 (.92)
Bulgaria	.38 (.21)	17	5	0	9.78 (5.90)	687.16 (339.57)	12.32 (3.75)
Croatia	1.37 (.48)	22	21	9	1.43 (.95)	1086.75 (393.70)	12.78 (3.18)
Cyprus	.84 (.33)	.	.	6	.14 (.15)	1571.79 (577.42)	5.65 (3.15)
Czech Rep	.53 (.16)	15	7	13	.23 (.14)	1426.20 (444.38)	6.72 (1.54)
Denmark	4.56 (.38)	42	25	14	.74 (.36)	3260.42 (983.65)	5.53 (1.36)
Estonia	5.43 (3.52)	12	5	10	.09 (.14)	866.31 (398.45)	10.14 (2.97)
Finland	2.55 (.76)	39	5	16	.11 (.23)	2492.32 (745.01)	9.40 (2.43)
France	.47 (.14)	18	18	17	1.06 (.43)	3166.65 (764.04)	9.85 (1.59)
Germany	1.76 (.35)	21	21	13	.84 (.27)	3379.03 (852.57)	8.26 (1.61)
Greece	2.02 (.68)	20	0	11	2.86 (1.34)	2107.53 (608.15)	12.02 (5.28)
Hungary	.31 (.09)	18	12	0	1.44 (1.68)	1249.51 (419.64)	8.24 (1.93)
Ireland	3.82 (.86)	21	13	11	1.20 (1.20)	2707.59 (1030.47)	8.22 (4.20)
Italy	1.26 (.62)	38	23	14	2.38 (1.15)	2433.98 (596.46)	9.51 (2.07)
Latvia	.79 (.50)	17	2	8	.05 (.05)	815.31 (361.48)	12.45 (3.48)
Lith.	1.35 (.58)	18	0	12	.16 (.15)	912.39 (443.29)	12.61 (3.96)
Lux	3.21 (1.41)	24	13	12	1.25 (1.05)	4799.57 (1665.42)	3.85 (1.24)
Malta	1.41 (.57)	26	18	7	1.15 (1.03)	1756.63 (606.99)	6.83 (.42)
Neth.	.71 (.11)	45	28	14	4.62 (1.64)	3539.84 (1352.02)	4.29 (1.43)
Norway	5.60 (1.28)	15	13	12	1.32 (.70)	4086.98 (1412.81)	3.65 (.69)
Poland	.66 (.11)	21	7	0	.34 (.31)	918.67 (397.09)	13.11 (4.10)
Portugal	.42 (.27)	36	14	14	1.18 (1.22)	1980.70 (608.79)	7.95 (3.63)
Romania	.09 (.06)	15	5	6	.58 (.57)	535.34 (312.28)	6.89 (.74)
Slovakia	.40 (.07)	16	0	14	.31 (.54)	1212.10 (645.92)	14.52 (2.93)
Slovenia	1.28 (.34)	23	18	8	5.02 (5.05)	1879.36 (573.54)	6.81 (1.32)
Spain	1.38 (.39)	23	15	17	1.00 (.58)	2162.85 (703.56)	16.32 (5.98)

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Country	Years of OST implementation				Control variables mean (SD)		
	DRDs	MMT	OST prison	HDBT	Heroin seizures	Expenditures on health	Unemp. rate
Sweden	2.58 (1.04)	46	8	14	.41 (.28)	2945.91 (821.48)	7.51 (1.51)
Turkey	.18 (.08)	0	0	0	14.17 (6.06)	601.84 (289.96)	9.36 (2.02)
UK	3.62 (.23)	45	8	14	2.07 (.78)	2457.97 (742.48)	6.41 (1.39)
Overall	1.81 (1.73)				1.84 (3.28)	2118.59 (1352.48)	6.78 (4.22)
Obs.	493						

Table 2

Dispersion in drug-related death count data

Drug-related deaths	
Mean cases	249.51
Variance	183,355.6
SD	428.18
Observations	493

Table 3

Negative binomial regression models of the effects of years of methadone maintenance implementation and control variables on overdose incidence rates (n = 28)

	Unadjusted		Adjusted		SE _{bs}
	IRR	SE	IRR	SE	
<i>Year and country fixed effects</i>					
MMT	.64	(.04)***	.61	.04***	.08***
Heroin seizures			1.01	.01	.01
Health expenditures			.91	.05	.06
Unemployment			.98	.006**	.009*
Observations	473		431		

* $p < .05$;
** $p < .01$;
*** $p < .001$

Table 4

Negative binomial regression models of the effects of years of prison opioid substitution treatment and control variables on overdose incidence rates (n = 22)

	Unadjusted		Adjusted		SE _{b₈}
	IRR	SE	IRR	SE	
<i>Year and country fixed effects</i>					
Prison OST	.93	*** (.009)	.90	.01 ***	.02 ***
Heroin seizures			1.01	.01	.02
Health expenditures			.98	.05	.07
Unemployment			1.01	.007	.009
Observations	370		332		

p < .001

Table 5

Negative binomial regression models of the effects of years of high-dose buprenorphine treatment (HDBT) and control variables on overdose incidence rates (n = 26)

	Unadjusted		Adjusted		SE _{ols}
	IRR	SE	IRR	SE	
<i>Year and country fixed effects</i>					
HDBT	.91	.01***	.92	.02***	.02**
Heroin seizures			1.00	.02	0.01
Health expenditures			.93	.05	0.07
Unemployment			.98	.008**	.01*
Observations	429		400		

* $p < .05$;
** $p < .01$;
*** $p < .001$