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Opiate- and Cocaine-Related Fatal Overdoses in Luxembourg from 1985 to 2011: A Study on Gender Differences

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Key Words
Drug use · Overdoses · Gender differences · Inequalities · Public health

Abstract
Background/Aim: We analysed gender differences in national fatal overdose (FOD) cases related to opiates and cocaine use between 1985 and 2011 (n = 340). ***Methods:*** Cross-examination of national data from law enforcement and drug use surveillance sources and of forensic evidence. Bivariate and logistic regression analysis of male/female differences according to sociodemographics, forensic evidence and drug use trajectories. ***Results:*** The burden of deaths caused by FOD on the general national mortality was higher for men ($PMR^{/100}$ = 0.55) compared with women ($PMR^{/100}$ = 0.34). Compared with their male peers, women were younger at the time of death (t = 3.274; p = 0.001) and showed shorter drug use careers (t = 2.228; p = 0.028). Heroin use was recorded more frequently in first drug offences of female victims (AOR = 6.59; 95% CI 2.97–14.63) and according to forensic evidence, psychotropic prescription drugs were detected to a higher degree in females (AOR = 2.019; 95% CI 1.065–3.827). ***Conclusion:*** The time window between the onset of illicit drug use and its fatal outcome revealed to be shorter for women versus men included in our study. Early intervention in female drug users, routine involvement of first-line healthcare providers and increased attention to use of poly- and psychotropic prescription drugs might contribute to prevent premature drug-related death and reduce gender differences.

Introduction

The latest estimates from UNODC [1] and WHO [2] refer to 172,000–245,000 drug-related deaths per year worldwide and approximately 50% are acute overdoses. Fatal overdose (FOD) caused by the use of illicit drugs in Europe accounts for an estimated 4% of premature deaths in young adults aged 15–39 years [3].

Knowing the prevalence of acute drug overdose cases is important in a public health perspective, but it demands more knowledge on determinants that might be at stake when it comes to assess the risk a person bears to fatally overdose on illicit drugs. External factors are numerous and obviously of diverse nature. The latter have been more or less extensively studied and include the overall health condition of drug users [4–6], the cumulative ef-

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fects and cross-reactions of heroin and other substances (particularly alcohol and other CNS depressants) in case of polydrug use [7–9], injecting drug use [10], dose tolerance levels [11] and the yet controversial impact of both purity [12, 13] and contamination of street drugs [8, 12, 13]. However, less is known about individual characteristics and the history of drug use of FOD victims.

Previous studies from various continents have shown that males are generally overrepresented in FOD cases [8, 11, 14–19]. Most recent research confirms this finding [20–23]. However, converging evidence suggests that the gender gap in illicit drug use has been declining over the last decades [23] and according to the World Drug Report 2012, there will be a greater risk of further increases in female illicit drug use, especially in developing countries, as conservative, social and cultural barriers break down and as gender equality increases [1]. This may have as a correlate that a higher proportion of female drug users will experience drug overdose in the future.

Even though previous cohort studies suggest higher overall mortality rates in females than in males if compared to their peers in the general population [standardised mortality ratios (SMR), irrespective of cause] [16, 24–27], females typically show lower mortality rates attributed exclusively to drug overdose fatalities [27–29].

The present paper focuses on the possible impact gender may have and how this impact varies according to sociodemographic and drug-use-related characteristics in FOD cases from 1985 (first national case) to the year 2011.

Methods

FOD is defined in the present study as a fatal acute adverse somatic reaction after the recent use of products containing opiates and/or cocaine, documented by toxicological and forensic evidence. In order to take best advantage of existing national data, a triangulation approach was chosen to cross-examining available data sources described below and thus to completing victims' profiles and life histories.

Drug Misuse Surveillance Data

The national drug monitoring system (RELIS) is operated by the Luxembourg focal point of the EMCDDA and indexes national drug-related contacts with both drug demand or drug supply reduction institutions in a single and integrated database. Indexed drug users are digitally anonymised by means of an encryption algorithm. The thus obtained individual RELIS code allows recognition of cases within single and between multiple data sources. The RELIS data protocol includes routine items on sociodemographics, educational, socioeconomic and health status, drug use histories and patterns, treatment records and contacts with the penal system.

Forensic Evidence

In case of a suspicious death case, the public prosecutor's office orders a toxicological investigation and an autopsy. Forensic reports contain data on substances detected in the organism and/or body fluids of the victim, physical aspects as well as a preliminary assessment of the association of detected substances and the occurrence of death. Autopsy reports may also contain some contextual information and elements of life history. Toxicological reports have been anonymised and made available to the research team by the toxicological Department of the National Laboratory of Health (LNS).

National Law Enforcement Records of FOD Cases

The competent judicial police authorities exhaustively list FOD cases occurring on the national territory after forensic confirmation. Toxicological evidence as well as case-related police reports are compiled for each case.

Cross-examination of data sources was possible as RELIS codes have been calculated and attributed to all FOD victims, previously de-identified. Matching cases could thus be reliably detected. Furthermore, toxicological and autopsy reports were attributed to respective cases by using date of birth and date of death of victims.

Given the lack of exhaustive descriptive national data on the population at risk (opiate and/or cocaine users) required to determine SMR, we calculated proportionate mortality ratios (PMRs) for males and females for all considered time periods. Z tests for proportions in independent groups were applied to assess whether PMRs differ significantly according to sex. Following a descriptive analysis of the total sample, a bivariate analysis was performed by means of χ^2, Fisher's exact and t tests in order to assess male/female differences with respect to demographic, socioeconomic and drug use history profiles of FOD victims. The Mann-Whitney U test was applied in case of non-normal distributions. Odds ratios (OR) and adjusted odds ratios (AOR) were calculated using logistic regression including predictor variables that significantly ($p < 0.05$) differed between males and females in the bivariate analysis. Observed effects according to sex were adjusted on age, duration of drug use career and administration route. Listwise deletion was chosen to eliminate cases with missing data on any of the predictors Statistical analysis was conducted using SPSS version 20.0.

Results

Figure 1, based on 3 years of moving average values, shows a continuous increase of national FOD rates from 1985 to a historical peak recorded between 1994 and 1996. From then onwards a discontinuous general downward trend has been observed, to reach a moving average of 3.1 cases per 100,000 inhabitants aged 15–64 years referred to the period 2009–2011.

In terms of male/female distribution, trends until the end of the 1980s are difficult to analyse given the statistically speaking low annual frequency of FOD cases. From 1991 to 2008, the mean ratio of female versus male victims has been varying between 14.7 and 21.3%, whereas the

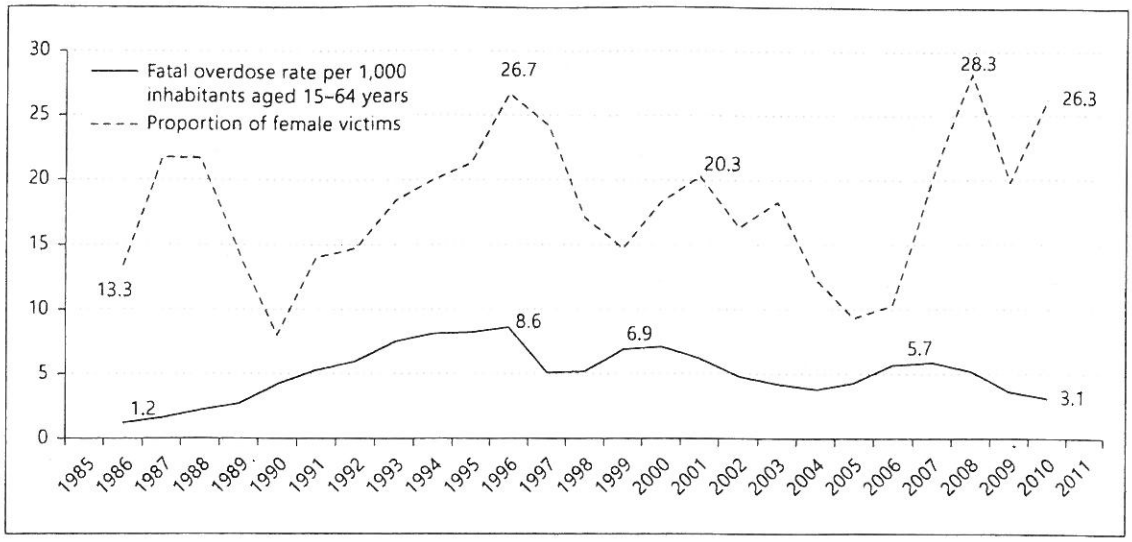

Fig. 1. Rates per 100,000 inhabitants aged 15–64 of FOD cases in the G.-D. of Luxembourg from 1985 to 2011 and proportion of female victims (3-years moving average values).

latter reached an unprecedented peak of 28.33% between 2008 and 2010.

In terms of gender differences, the proportional burden of FOD deaths on the overall national mortality has contributed to a higher extent to the male mortality between 1985 and 2011 ($Z = 11.66$; $p < 0.01$).

Table 1 provides an overview of victims' characteristics according to sex from 1985 to 2011. No significant changes in the sex ratio of victims were observed and women were younger than men at the time of death ($t = 3.274$; $p = 0.001$). The age range of victims was 15–60 years. 30.3% of male and 28.5% of female victims were between 25 and 29 years, although women were more likely to die from FOD before the age of 20 years (AOR = 4.374; 95% CI 1.76–10.86).

The unemployment rates observed in female and in male victims are almost identical and no association between occupational status of professionally active victims and sex was found ($\chi^2 = 9.637$; $p = 0.210$). In terms of financial income, women were more likely to depend on sexwork ($p = 0.001$).

The preferential illicit drug during lifetime of decedents was heroin and no significant male/female differences according to preferred substances have been observed. In contrast, toxicological evidence revealed that heroin was more likely to be detected in male FOD victims (AOR = 2.955; 95% CI 1.090–8.008), while psychotropic prescription medications were found to a significantly higher degree in females (AOR = 2.019; 95% CI 1.065–3.827).

As far as administration routes are concerned, men had insignificantly higher rates of injecting drug use than women ($\chi^2 = 1.376$; $p = 0.241$), whereas female victims were more likely to show polydrug use before their FOD (AOR = 7.832; 95% CI 1.010–60.937).

We also analysed drug-use-related time variables of victims and found shorter durations for female versus male victims between first use of any illicit drug and death ($t = 2.228$; $p = 0.028$), between first contact with a health or law enforcement service/authority and the FOD ($t = 2.609$; $p = 0.010$) and between the first police record for a drug-related offence of the victim and the occurrence of the FOD ($t = 2.492$; $p = 0.013$).

Law enforcement data showed that heroin was involved in first police records of 81.6% of women who deceased from FOD, compared with 41.1% for male decedents (AOR = 6.59; 95% CI 2.97–14.63). Also, 61.5% of female victims had never been in prison versus 35.5% of male FOD victims, although the adjusted OR does not show statistical significance for prison history (AOR = 1.83; 95% CI 0.807–4.15; $p = 0.148$) (table 2).

The following variables were also included in the analysis, although they were not further addressed as no significant gender differences were found and as far as they were not relevant to the interpretation of study results: nationality, civil status, educational status, housing situation (of victims), professional status of father or legal tutor and substance abuse in parents.

Table 1. PMRs and characteristics of FOD victims stratified by gender from 1985 to 2011 (valid % if not otherwise specified) and statistical significance of gender differences (p value)

	Male	Female	Total	p value
Proportionate mortality ratios (PMR/100) (n = 340)	0.55	0.12	0.34	**
Demographics and socioeconomic status				
Gender (n = 340)	81.5	18.5	100	**
Age (n = 340)				
Age distribution				
15–19 years	4.3	15.9	6.5	**
20–24 years	20.6	27.0	21.7	n.s.
25–29 years	30.3	28.5	30.0	n.s.
30–34 years	19.2	12.7	18.0	n.s.
35–39 years	11.9	11.1	11.7	n.s.
40–44 years	8.3	4.8	7.4	n.s.
45–49 years	4.0	0.0	3.5	n.s.
50–54 years	1.0	0.0	0.9	n.s.
>54 years	0.4	0.0	0.3	n.s.
Mean age at time of death, years	30.1±7.9	26.6±6.8	29.4±7.7	**
Occupational status				
Unemployment (n = 216)	77.1	78.0	77.3	n.s.
Labour status (n = 68)				
Regular employment	28.0	41.7	30.6	n.s.
Occasional employment	46.0	8.3	38.7	**
Invalidity status	14.0	8.3	12.9	n.s.
Homemaker	2.0	8.3	3.2	n.s.
Others (student, trainee, retired, disabled)	10.0	33.4	14.6	n.s.
Source of revenue				
Primary livelihood (n = 195)				
Social minimum income	31.1	26.5	30.3	n.s.
Unemployment benefit	11.2	11.8	11.3	n.s.
Parents	8.1	11.8	8.7	n.s.
Spouse/partner	2.5	8.8	3.7	n.s.
Own salary	16.1	20.6	16.9	n.s.
Financial reserves/maintenance allowance	1.9	0.0	1.5	n.s.
Disability allowance	4.3	2.9	4.1	n.s.
Sex work	0.0	11.8	2.1	**
Delinquency	1.9	0.0	1.5	n.s.
Drug dealing	8.1	2.9	7.2	n.s.
Begging	14.3	2.9	12.3	n.s.
Others	0.5	0.0	0.4	n.s.
Drug-use-related and forensic data				
Primary drug[a] (n = 182)				
Heroin	88.5	88.2	88.5	n.s.
Cocaine	6.1	8.9	6.6	n.s.
XTC	2.0	0.0	1.6	n.s.
Cannabis	1.4	2.9	1.6	n.s.
Others	2.0	0.0	1.7	n.s.
Administration route				
Injection (n = 324)	93.1	88.7	92.3	n.s.
Polydrug use[a] (n = 189)	82.4	97.5	91.5	**
Autopsy: detected substances[b] (n = 340)				
Heroin	92.4	82.5	90.6	**
OST drugs	14.1	19.1	14.8	n.s.
Cocaine	10.1	11.1	9.7	n.s.
Cannabis	3.6	0.0	2.9	n.s.
Psychotropic prescription drugs	31.8	44.4	34.2	*
Other psychoactive substances	0.4	0.0	0.3	n.s.
Drug use and penal histories				
Mean duration: first illicit drug use – FOD, years (n = 135)	16.5±8.1	12.5±7.0	15.8±7.7	*
Mean duration: first contact with specialised agencies – FOD, years (n = 297)	9.1±6.7	6.5±5.9	8.6±6.6	*
Penal history				
Known by law enforcement authorities before death (n = 340)	86.6	79.4	85.3	n.s.
Mean duration between first record of drug-related offence and FOD, years (n = 289)	9.0±6.8	6.4±6.1	8.5±6.7	*
Illicit substances involved in first recorded drug law offence (n = 280)				
Heroin	41.1	81.6	51.4	**
Cocaine	6.9	8.2	7.1	n.s.
Amphetamines	5.2	0.0	4.3	n.s.
XTC	0.9	4.1	1.1	n.s.
LSD	4.8	6.1	5.0	n.s.
Cannabis	62.8	34.7	57.9	n.s.
Prison sentences (n = 198)				
One	34.6	20.5	31.8	n.s.
Multiple	28.9	17.9	26.8	n.s.
None**	36.5	61.6	41.4	**

* Significant differences according to gender with $p < 0.05$. ** Significant differences according to gender with $p < 0.01$. n.s. = Statistically not significant: $p > 0.05$.

[a] Applied definitions are based on standards of the European Monitoring Centre on Drugs and Drugs Addiction [40]. [b] Alcohol excluded.

Discussion

Our findings confirm that polydrug use, and thus polydrug toxicity, are contributory factors to FOD, but do also show that female overdose victims included in our study present a higher propensity to multiple drugs' use than their male counterparts. The relative contributory impact of polydrug use on the overall overdose risk seems to be more substantial in women, even more so in the light of higher observed injection rates in male victims. Although heroin was the preferential drug of both male and female FOD victims, toxicological analyses have detected psychotropic prescription medications in a higher proportion of deceased women.

Table 2. OR and AOR of p < 0.5 baseline variables according to gender effect

Baseline variables (p < 0.05)	Reference	OR	95% CI	p value	AOR	95% CI	p value
Age <20 years	F vs. M	4.167	1.712–10.414	0.002	4.374	1.761–10.862	0.001
Lifetime prison stay	M vs. F	2.786	1.354–5.732	0.005	1.830	0.807–4.148	0.148
Heroin involved in first police record	F vs. M	4.847	2.309–10.174	<0.001	8.619	3.564–20.844	<0.001
Polydrug use	F vs. M	9.046	1.194–68.518	0.023	7.832	1.010–60.937	0.049
Heroin use confirmed by toxicological evidence	M vs. F	2.579	1.173–5.671	0.018	2.955	1.090–8.008	0.033
Use of psychotropic prescription drugs confirmed by toxicological evidence	F vs. M	1.858	1.067–3.235	0.028	2.019	1.065–3.827	0.031

F = Female FOD victims; M = male FOD victims.

Previous research results suggest that teenage girls, but also adult women, are likelier than their male peers to have used psychotropic prescription drugs for non-medical reasons [29–30] and that females are twice as likely as males to become addicted to sedative, hypnotics or anti-anxiety drugs [30]. Research on co-occurring psychiatric disorders also has revealed higher rates of affective and anxiety disorders in female alcohol [31], cocaine [32] and opioid [33] abusers compared with their male peers. Women with a prescription drugs' use profile engaging in additional use of illicit drugs thus may bear greater risks of FOD occurring at an earlier stage than men due to initial polytoxicity. In other words, these women show polydrug use at the very moment they use their first illicit drug and thus are exposed to a higher risk potential and a shorter 'drug user life expectancy' as results from the present study suggest.

We also found that female FOD cases included in our study were younger and had shorter drug use histories than male victims. Three measures assessing the duration between first illicit drug use, first drug-related institutional contact, first drug-related offence record and the moment of death showed shorter 'careers' for women. These findings converge with previous research findings suggesting that women progress faster from first to regular use and to first treatment episodes [34], and that most women who enter treatment have used substances for a shorter time period, whereas their addictions had become acute quicker than in their male counterparts.

Our study further revealed that the involvement of heroin already in the first law offence record of women was twice as frequent as in male victims. Not only the progression from the initiation of illicit drug use to dependence and first treatment appears to be accelerated in women, the latter also typically encounter more severe medical, behavioural, psychological and social problems due to their substance abuse than male addicts at treatment onset. Some authors refer to this phenomenon as 'telescoping' that may be modulated by both biological and psychosocial factors [34–36].

Male victims served prison sentences during their lifetime to a consistently higher degree than their female counterparts. An exploratory comparison with national problem drug users (PDU) surveillance data between 2002 and 2011 revealed that living male PDU also tend to show more frequent prison records than female users [37]. Interestingly, however, the observed gender differences in imprisonment rates are much weaker (10–15%) in the overall national PDU population compared with FOD cases. Even though female PDU typically show lower lifetime imprisonment rates than male PDU, they tend to show higher rates than female FOD victims. Thus, female FOD victims may be less likely to show lifetime incarceration than female PDU monitored at the national level. This finding should be further addressed by including the potential effects of age, duration of drug use and previous contacts with law enforcement authorities to determine if an independent gender effect is at stake.

The window of opportunity for intervention between the onset of drug use and its fatal ending tends to be shorter for women compared with men. Our results suggest that early intervention in female drug users might be necessary and that enhanced attention should be paid to polydrug use patterns including the use of psychotropic prescription drugs as well as the existence of a co-occurring psychiatric disorders' history in women. Gender-specific drug-care programmes should also assess whether mood or anxiety disorders in patients do occur independently of substance use episodes in order to conceive treatment follow-up protocols to be applied during absti-

nence periods to reduce relapse and high-risk contexts for FOD. As women typically undergo more frequent doctor visits than men [38], latest evidence on gender-specific overdose risks factors should be routinely provided to general practitioners, gynaecologists and harm reduction agencies in order to promote early involvement of first-line healthcare providers.

A fatal drug overdose is not a self-contained event. It may be better described as an encounter of harmful circumstances that have been culminating from different starting points through various pathways into a deadly end. Although drug-related counselling and treatment providers have increasingly recognised the importance of targeted approaches and responses for both male and female users in need, drug-related mortality prevention measures tailored according to gender are still scarce [39].

The aim of present study was limited to the analysis of gender differences in FOD cases and, as such, does not provide supplementary evidence on risk or protective factors of drug-related mortality in the overall population of drug users. Furthermore, data triangulation did allow improving previously available national data on FOD cases; nonetheless the final dataset contained a series of missing values, which reduces the explanatory power of our findings.

Further studies, based on cohort or case-control designs, analysing more comprehensively possible determinants of FOD according to gender, should be conducted, with the final aim to save life, generate years of life without major impairments and enhance evidence-based drug policy planning in continuously evolving social and economic realities.

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Disclosure Statement

The authors have no conflicts of interest to disclose.

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