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# Trends in drug poisoning deaths, by sex, in Ireland: a repeated cross-sectional study from 2004 to 2017

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# Trends in drug poisoning deaths, by sex, in Ireland: a repeated cross-sectional study from 2004 to 2017


## Abstract

**Objectives** Drug poisoning deaths are increasing globally and despite variation by sex, evidence on sex-specific comparisons is lacking. The aim of this study is to examine sex differences in age-standardised rates of overall and drug-specific drug poisoning deaths, in Ireland between 2004 and 2017.

**Design** A repeated cross-sectional study.

**Setting** Drug poisoning deaths in Ireland

**Participants** Data from the National Drug-Related Deaths Index and pharmacy claims database, 2004 to 2017.

**Outcome measures** Primary outcome: all drug poisoning deaths. Secondary outcomes: drug poisoning deaths involving (1) CNS depressants; (2) ≥ 2 CNS depressants; and (3) individual drug classes (e.g. prescription opioids, benzodiazepines, antidepressants, alcohol, cocaine and heroin). Joinpoint Regression was used to examine trends, stratified by sex, in the rate of age-standardised drug poisoning deaths (2004 to 2017); change points over time and average annual percentage changes (AAPCs) with 95% confidence intervals (CI).

**Results** Increased age-standardised rate for all drug poisoning deaths from 13.50 (95% CI 11.35-15.66) per 100,000 in 2004 to 16.03 (95% CI 13.92-18.14) per 100,000 in 2017 was mainly driven by increasing deaths among men (AAPC 2.6% [95% CI, 0.2 - 5.1]) with no significant change observed among women. Deaths involving CNS depressant drugs showed a similar trend to all drug poisoning deaths however, deaths involving ≥ 2 CNS depressants increased for men (AAPC 5.6% [95% CI, 2.4 - 8.8]) and women (AAPC 4.0% [95% CI, 1.1 -

6.9]). Drugs with the highest significant AAPC increases for men were: cocaine (7.7% [(95% CI, 2.2 - 13.6]), benzodiazepines (7.2% [(95% CI, 2.9 - 11.6]), antidepressants (6.1% [(95% CI, 2.4 - 10.0]), and prescription opioids (3.5% [(95% CI, 1.6 - 5.5]). For women the highest AAPC was for antidepressants (4.2% [(95% CI, 0.2 - 8.3]), benzodiazepines (3.3% [(95% CI, 0.1 - 6.5]), and prescription opioids (3.0% [(95% CI, 0.7 - 5.3]).

**Conclusion** There were differences in the drugs implicated in death between men and women. Policy response should include increased prescription monitoring programmes, education and practical harm reduction information on polydrug use, especially CNS depressant drugs.

**Key words** Drug; poisoning; death; men; women; sex; gender

## Article Summary

### *Strengths and limitation of this study:*

- Access to national mortality data from four different sources provides more robust data and strengthens the completeness of the data on drug poisoning deaths.
- Use of mortality data in addition to prescription data enabled assessment of the relationship between trends in prescribing and poisoning deaths involving specific drugs.
- Limitations of this study include the reliance on individual Coroners to implicate specific drugs in poisoning deaths, which can be challenging when multiple drugs are present on a toxicology report.
- Information on whether the drugs were prescribed to the individual is frequently not available in the sources of data, which limits the assessment of illicit use of these drugs and the impact of illicit drugs on these deaths.

- Lack of data on private prescription drugs dispensed stratified by sex, limits analysis to those dispensed through the GMS/PCRS scheme and so analysis does not include private prescriptions.

## Introduction

Drug poisonings are a leading cause of avoidable death worldwide, with rates increasing globally. National trends from the United States (U.S.) show that drug poisoning deaths have increased rapidly in recent years, with a 15% increase per year during 2013 and 2017 (1). During this period drug poisoning death rates increased in most states in the U.S., primarily due to synthetic opioids (2). Drug poisoning deaths involving cocaine and psychostimulants have also increased in the U.S. (3, 4). Accidental drug poisonings are predicted to be a leading cause of premature deaths in the U.S over the next decade, especially among women (5). Drug poisoning deaths have also increased in Australia since 2006, with opioids being the most common drug group involved in these deaths (6).

Similar patterns have been observed across Europe. For example, the number of drug poisoning deaths recorded in England and Scotland in 2017 was the highest ever recorded, with opioid-related deaths representing the leading cause of these deaths (7). The European Monitoring Centre of Drugs and Drug Addiction (EMCDDA) also reported an increase in drug poisoning deaths between 2012 and 2018 in Europe, increasing from an estimated 17 deaths per million population aged 15-64 in 2012 (8) to 22.6 deaths per million population aged 15-64 years in 2018 (9). While opioids, often heroin, are involved in approximately 8 out of every 10 drug poisoning deaths reported in Europe, post-mortem toxicology analyses of poisoning cases suggest that multiple drug toxicity is implicated in most cases (9).

While sex differences in drug poisoning deaths have emerged in recent years (10) most of the available evidence fails to account for variation by sex regarding drugs involved in drug poisoning deaths (11). Consequently as drug poisoning deaths are dominated by deaths among men, specific circumstances associated with drug poisoning deaths among women may be masked by combining trends for men and women. For example, in the U.S., a higher

risk of drug poisoning death among young men relative to young women has been reported to be attributed to heroin and synthetic drugs (10). In contrast, in both the U.S. and Scotland, risk of drug poisoning deaths among older women were attributed to prescription opioids, antidepressants (12, 13); and unspecified drugs (10). Also, sex-specific differences in pharmacokinetics for certain drugs, including CNS depressants such as opioids (14), pregabalin and benzodiazepines (15), suggest that CNS depressant drugs may be impacting more on polydrug poisoning deaths among women.

Furthermore, although the absolute number of drug poisoning deaths are higher in men, epidemiological trends in Europe and the U.S. suggest the rate of drug poisoning deaths among women is increasing at a higher rate relative to men (9, 16), especially in relation to intentional drug poisoning deaths (17).

The aim of this study is to examine sex differences in age-standardised rates of overall drug poisoning deaths, and drug-specific deaths in Ireland between 2004 and 2017. Drug specific deaths include: drug poisoning deaths involving (1) CNS depressants; (2) ≥ 2 CNS depressants; (3) and individual drug classes (e.g. prescription opioids, benzodiazepines, antidepressants, alcohol, cocaine and heroin).

This study also examines the association between dispensing rates of prescribed medications commonly implicated in drug poisoning deaths (specifically, opioids, benzodiazepines and antidepressants), and drug poisoning deaths involving these agents.

## Methods

The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist for cross-sectional studies (18) was used as a guide to structure this repeated cross-sectional study. The study was approved by the Royal College of Surgeons in Ireland Research Ethics Committee on 1st May 2018 REC 1542.

## *Data sources*

*Drug poisoning deaths*

Design: Repeated cross-sectional study.

This study includes anonymized individual level data on all poisoning deaths in Ireland as recorded by the National Drug-Related Deaths Index (NDRDI) for years of death 2004 to 2017 inclusive. The NDRDI is an epidemiological database which records all poisoning deaths by drugs and/or alcohol (19). It follows the EMCDDA standard protocol to collect data on drug-related deaths which is used in 28 European countries, Norway and Turkey (20). To ensure completeness, data from several sources are collected and cross-checked to avoid duplication. Coronial files are the main data source for the NDRDI. Coronial data is collected for the purpose of death investigation, thus not primarily for research, however coronial data has been recognised as a rich source of data for monitoring drug poisoning deaths (21). Other NDRDI data sources include; the General Mortality Register via the Central Statistics Office (CSO), acute hospitals data (via the Hospital In-patient Enquiry System [HIPE]) and the national opioid agonist treatment (OAT) register, the Central Treatment List (CTL). Further details on the NDRDI methodology can be found elsewhere (19). The methodology for collecting poisoning deaths did not change over the study period.

The NDRDI's definition of a poisoning death is a death directly due to the toxic effect of one or more drugs (including alcohol) on the body, as directed by the Coroner on the certificate of death registration and/or the record of verdict. Up to six drugs implicated in drug poisoning deaths by the Coroner are included in the NDRDI and using multi response analysis we included these drugs in the analysis. Data on deaths which included specific drugs and drug groups; opioids, benzodiazepines, antidepressants, Z-drugs, pregabalin, alcohol and cocaine,

were extracted from the NDRDI for this study. These are the main drugs implicated in poisoning deaths in Ireland (22).

*National opioid agonist treatment (OAT) register*

In 1998 the Misuse of Drugs (Supervision of Prescription and Supply of Methadone) Regulations were introduced in Ireland, which involved the establishment of a national register, the Central Treatment List (CTL). All patients in receipt of OAT are listed on the CTL, with each patient linked to one specific prescriber and a single dispensing site. In addition to aggregate data on the number of people registered on the CTL during the study period, data on the number of individuals who died while registered as being in treatment on the CTL during the study period were also extracted.

*Pharmacy claims data*

Aggregate level (by age, gender, year and drug class) pharmacy claims data related to prescription drugs only, including prescription opioids, benzodiazepines and antidepressants were received from the Irish Health Service Executive (HSE) Primary Care Reimbursement Services (PCRS). This included only those with full eligibility for the General Medical Services (GMS) scheme at any time during 2004 to 2017 inclusive. The HSE-PCRS pharmacy claims database contains details of all prescription medications dispensed to GMS eligible patients in primary care but does not include data on private prescriptions dispensed. Eligibility for the GMS prescription scheme is mainly through means-testing and age; therefore, it over-represents the more socially deprived and younger and older aged populations in Ireland. All claims are coded using the WHO's Anatomical Therapeutic Chemical (ATC) classification. The HSE-PCRS database contains basic demographic information including age, sex and region of residence (23). As of 2015, almost 40% of the Irish population were covered by the GMS scheme (23).

Data on all eligible individuals ≥16 years of age who were prescribed the following drugs; opioids, benzodiazepines and/or antidepressants, were included in the study. For opioids, the number of people registered on the CTL and in receipt of OAT, either methadone or buprenorphine, were combined with the number of people prescribed opioids on the HSE-PCRS database (ATC codes [N02AA01, N02AA03, N02AA05, N02AA08, N02AB02, N02AB03, N02AE01, N02AX02, N02AX05 or N02AX06]) during the study period. The number of people prescribed benzodiazepines (N05CD, N05BA or N03AE01), and antidepressants (N06AA, N06AB, N06AF, N06AG or N06AX), were also extracted from the HSE-PCRS database.

### *Study variables*

The primary outcome was drug poisoning deaths defined as a death directly due to the toxic effect of one or more drugs (including alcohol) on the body. The secondary outcomes of interest were drug poisoning deaths involving (1) any CNS depressant drugs; (2) two or more CNS depressants drugs; and (3) individual drug classes: prescribed opioids, benzodiazepines, antidepressants, alcohol, cocaine and heroin.

For poisoning deaths involving CNS depressant drugs, any deaths involving opioids, benzodiazepines, alcohol, pregabalin and/or Z-drugs were combined into deaths due to 'CNS depressant drugs'. Gender, year of death and age groups (15-29, 30-44, 45-59 and ≥60 years) were also included.

### *Statistical analysis*

All analyses of trends were examined overall and separately for men and women.

*Drug poisoning deaths*

Irish general population estimates were extracted from the CSO (24) for calculation of rates of poisoning deaths per 100,000 population. The GMS eligible population for those aged 16 years and older was extracted from the PCRS annual reports (25). The European Standard Population (ESP)(26) was used to calculate age-standardised rates (ASR).

Trends in age-standardised mortality rates (ASMR) for all drug poisoning deaths and the specific drug groups mentioned above were examined by males and females while adjusting for age. Mortality rates for each year of the study period were calculated per 100,000 of the general population based on national census and projected population figures (24), standardised to the European Standard Population (ESP) (26). Rates are presented with 95% Confidence Intervals (CI).

Joinpoint Regression Program version 4.8.0.1 (27) was used to examine the overall trends in age-standardised rates from 2004 to 2017, expressed as annual percentage changes (APCs), with any changes in trends over time expressed as an average annual percentage changes (AAPCs). The AAPC is a summary measure which describes the average of the APCs over time. Joinpoint regression detects if there are any statistically significant trend changes in the overall drug poisoning death rates over time and other specific drug poisoning death rates involving CNS depressant drugs and for each of the drug classes described.

*Association with prescribing patterns*

Age-standardised prescription rates (ASPR) per 1,000 of GMS eligible population for each calendar year were standardised using the relevant age categories from the ESP. For prescription opioids, data received from the CTL was not available by age stratification, therefore, crude rates were used for this drug group.

Ecological analysis of the aggregated data, using annual age-standardised rates for drug poisoning deaths and prescription data, was performed using linear regression to examine the

relationship (beta regression coefficient, 95% CI) between trends in ASPR for benzodiazepines and antidepressants or crude rates for prescription opioids and drug poisoning death rates involving these drugs. All analyses were stratified by sex.

Significant at $p < 0.05$ is assumed. Data was analysed using Joinpoint Regression Program (Version 4.8.0.1 National Cancer Institute, U.S.), and SPSS version 22 (IBM SPSS Statistics for Windows, v.22.0. Armonk, NY: IBM Corp.).

## Results

### *All drug poisoning deaths*

For the study period, 2004 to 2017 there were 4,993 drug poisoning deaths recorded in Ireland. In 2004 there were 266 drug poisoning deaths (175 [66%] men; 91 [34%] women), representing an ASMR of 13.5 deaths per 100,000 (8.5 deaths per 100,000 men and 5.0 deaths per 100,000 women). By 2017 there were 376 drug poisoning deaths, an increase of 41.4%, (263 [70%] men; 113 [30%] women) occurring at an ASMR of 16.0 deaths per 100,000 (11.5 deaths per 100,000 men and 4.8 deaths per 100,000 women). The rate of all drug poisoning deaths among men from 2004 to 2017 increased at an AAPC of 2.6% (95% CI, 0.2 - 5.1) (Table 1), however there was no significant change among women for the same period (Table 2). Joinpoint regression analysis identified an accelerated increase in drug poisoning deaths among men in earlier years (2004 – 2007) with no significant change in the latter years 2007 – 2017 (Table 1).

The ASMR for 2004 and 2017 by any CNS depressant drugs, two or more CNS depressant drugs, individual drug classes and individual drugs, stratified by sex are also presented in Tables 1 & 2.

**Table 1: Age-standardised rates (standardised to the European Standard Population) of drug poisoning deaths, per 100,000 of the general population, with APCs and AAPCs, 2004 to 2017, among men in Ireland**

| Men | | | | | |
|---|---|---|---|---|---|
| | | *Age-standardised rates per 100,000 population* | | | |
| **Drug group** | **Period** | **2004** | **2017** | **APC (95% CI) %** | **AAPC (95% CI) %** |
| All drug poisoning deaths | 2004-2007 | 8.51 | 11.50 | 13.2 (1.6 to 26.1)*** | |
| | 2007-2017 | 11.50 | 11.19 | -0.3 (-1.9 to 1.2) | |
| | 2004-2017 | 8.51 | 11.19 | | 2.6 (0.2 to 5.1)*** |
| CNS depressant drugs | 2004-2008 | 6.91 | 9.75 | 10.1 (3.3 to 17.2)*** | |
| | 2008-2017 | 9.75 | 8.57 | -1.1 (-2.7 to 0.5) | |
| | 2004-2017 | 6.91 | 8.57 | | 2.2 (0.3 to 4.2)*** |
| 2 or more CNS depressant drugs | 2004-2011 | 2.29 | 5.67 | 10.8 (5.9 to 16.0)*** | |
| | 2011-2017 | 5.67 | 4.95 | -0.2 (-5.4 to 5.3) | |
| | 2004-2017 | 2.29 | 4.95 | | 5.6 (2.4 to 8.8)*** |
| Prescription opioids | 2004-2017 | 2.76 | 3.96 | 3.5 (1.6 to 5.5)*** | 3.5 (1.6 to 5.5)*** |
| Benzodiazepines | 2004-2017 | 1.56 | 3.96 | 7.2 (2.9 to 11.6)*** | 7.2 (2.9 to 11.6)*** |
| Antidepressants | 2004-2017 | 0.70 | 1.50 | 6.1 (2.4 to 10.0)*** | 6.1 (2.4 to 10.0)*** |
| Alcohol | 2004-2017 | 4.12 | 3.83 | -0.9 (-3.2 to 1.4) | -0.9 (-3.2 to 1.4) |
| Cocaine | 2004-2006 | 0.64 | 2.19 | 107.3 (56 to 175.6)*** | |
| | 2006-2010 | 2.19 | 0.64 | -25 (-35.1 to -13.3)*** | |
| | 2010-2017 | 0.64 | 1.58 | 9.9 (5.6 to 14.3)*** | |
| | 2004-2017 | 0.64 | 1.58 | | 7.7 (2.2 to 13.6)*** |
| Heroin | 2004-2006 | 0.61 | 2.70 | 83.4 (-33.7 to 407.7) | |
| | 2006-2017 | 2.70 | 2.64 | -1.1 (-4.5 to 2.5) | |
| | 2004-2017 | 0.61 | 2.64 | | 8.8 (-5.2 to 24.9) |

Variables significant at ***p < 0.001, ** p < 0.01, * p < 0.05.

**Table 2: Age-standardised rates (standardised to the European Standard Population) of drug poisoning deaths, per 100,000 of the general population, with APCs and AAPCs, 2004 to 2017, among women in Ireland**

| Women | | | | | |
|---|---|---|---|---|---|
| | | *Age-standardised rates per 100,000 population* | | | |
| **Drug group** | **Period** | **2004** | **2017** | **APC (95% CI) %** | **AAPC (95% CI) %** |
| All drug poisoning deaths | 2004-2017 | 4.99 | 4.84 | -0.5 (-2.2 to 1.2) | -0.5 (-2.2 to 1.2) |
| CNS depressant drugs | 2004-2015 | 4.20 | 4.61 | -0.7 (-3.5 to 2.1) | |
| | 2015-2017 | 4.61 | 7.67 | 39.0 (3.2 to 87.2)*** | |
| | 2004-2017 | 4.20 | 7.67 | | 4.5 (0.0 to 9.3) |
| 2 or more CNS depressant drugs | 2004-2017 | 2.08 | 2.11 | 4.0 (1.1 to 6.9)*** | 4.0 (1.1 to 6.9)*** |
| | 2004-2017 | | | | |
| Prescription opioids | 2004-2017 | 1.54 | 2.02 | 3.0 (0.7 to 5.3)*** | 3.0 (0.7 to 5.3)*** |
| Benzodiazepines | 2004-2017 | 1.70 | 1.67 | 3.3 (0.1 to 6.5)*** | 3.3 (0.1 to 6.5)*** |
| Antidepressants | 2004-2017 | 1.71 | 1.40 | 4.2 (0.2 to 8.3)*** | 4.2 (0.2 to 8.3)*** |
| Alcohol | 2004-2017 | 2.72 | 1.65 | -4.0 (-5.8 to -2.1)*** | -4.0 (-5.8 to -2.1)*** |
| Cocaine | 2004-2008 | 0.08 | 0.45 | 61.1 (14.0 to 127.6)*** | |
| | 2008-2011 | 0.45 | 0.04 | -56.6 (-84.1 to 18.6) | |
| | 2011-2017 | 0.04 | 0.58 | 53.8 (26 to 87.8)*** | |
| | 2004-2017 | 0.08 | 0.58 | | 16.5 (-6.3 to 44.8) |
| Heroin | 2004-2017 | 0.09 | 0.47 | 7.0 (-0.2 to 14.6) | 7.0 (-0.2 to 14.6) |

Variables significant at ***p < 0.001, ** p < 0.01, * p < 0.05.

**Table 3: Age-standardised rates (standardised to the European Standard Population) of drug poisoning deaths, per 100,000 of the general population, 2004 to 2017, among all drug poisoning deaths in Ireland and ratio of men to women.**

| Total drug poisoning deaths | | | | |
|---|---|---|---|---|
| | *Age-standardised rates per 100,000 population (95% CI)* | | Ratio of men to women | |
| **Drug group** | **2004** | **2017** | **2004** | **2017** |
| All drug poisoning deaths | 13.50 (11.35-15.66) | 16.03 (13.92-18.14) | 1.7:1 | 2.3:1 |
| CNS depressant drugs | 11.11 (9.06-13.15) | 16.24 (14.25-18.22) | 1.6:1 | 1.1:1 |
| 2 or more CNS depressant drugs | 4.37 (2.75-5.99) | 7.05 (5.35-8.75) | 1.1:1 | 2.3:1 |
| Prescription opioids | 4.30 (2.72-5.89) | 5.98 (4.34-7.62) | 1.8:1 | 2:1 |
| Benzodiazepines | 3.26 (1.75-4.77) | 5.63 (4.03-7.24) | 1:1 | 2.4:1 |
| Antidepressants | 2.41 (1.02-3.79) | 2.90 (1.49-4.30) | 0.4:1 | 1.1:1 |
| Alcohol | 6.85 (5.00-8.69) | 5.47 (3.84-7.10) | 1.8:1 | 2.3:1 |
| Cocaine | 0.72 (-0.18-1.61) | 2.15 (0.90-3.41) | 8.5:1 | 2.7:1 |
| Heroin | 0.70 (-0.41-1.80) | 3.11 (1.77-4.45) | 6.7:1 | 5.6:1 |

### *CNS depressant drugs*

The rate of drug poisoning deaths involving any CNS depressant drugs increased from a rate of 11.1 deaths per 100,000 (95% CI 9.1 - 13.2) in 2004 to a rate 16.2 deaths per 100,000 (95% CI 14.3 - 18.2) in 2017 (Table 3). There was an AAPC increase of 2.2% (95% CI, 0.3 – 4.2) for men with an accelerated increase noted for the period 2004 to 2008, however, when drug poisoning deaths included two or more CNS depressant drugs, men showed a higher AAPC at 5.6% (95% CI, 2.4 – 8.8) (Table 1).

For women who died of drug poisoning deaths involving any CNS depressant drugs, no significant AAPC was observed, however when two or more CNS depressant drugs were involved in the death, there was an AAPC of 4% (95% CI, 1.1 – 6.9) (Table 2).

Benzodiazepines were the main drug group implicated in all (men and women combined) drug poisoning deaths involving two or more CNS depressant drugs, implicated in 76% of these deaths.

### *Prescription Opioids*

All drug poisoning deaths involving prescription opioids, of which 61% consisted of methadone, have increased over time (Table 3) with similar AAPC for both men (3.5% [95% CI, 1.6 - 5.5]) and women (3.0% [95% CI, 0.7 - 5.3]) and no change points noted (Tables 1 & 2). Forty three percent of deaths involving methadone, were among people prescribed methadone as part of OAT. Although fewer women are in receipt of OAT relative to men, almost two in every three women (63%) who had methadone implicated in their death were in receipt of prescribed methadone for OAT. In contrast, just over one in every three (36%) men, where methadone was implicated in their poisoning death, were in receipt of prescribed methadone for OAT.

A relationship, albeit weak and not statistically significant ($\beta = 0.098$, [95% CI -0.020, 0.027], $p > 0.05$) was observed among women in receipt of prescription opioids through the CTL and/or HSE-PCRS pharmacy claims combined and the ASMR per 100,000 where prescription opioids were involved in drug poisoning deaths, for the period 2004 to 2017 (Figure 1).

Insert Figure 1

### *Benzodiazepines*

The rate of drug poisoning deaths involving benzodiazepines increased over the reporting period at an AAPC of 7.2% (95% CI, 2.9 – 11.6) among men (Table 1) and 3.3% (95% CI, 0.1 – 6.5) among women (Table 2) with no change points observed among men or women (Table 1 & Table 2).

For benzodiazepines a negative relationship was observed between prescribing data and drug poisoning deaths for both men ($\beta = -0.077$, [95% CI -0.116, -0.018], $p < 0.05$) and women ($\beta$

= -0.016, [95% CI -0.031, 0.000], p > 0.05), albeit not statistically significant for women, for the period 2004 to 2017 (Figure 2).

Insert Figure 2

### *Antidepressants*

For both men (6.1% [95% CI, 2.4 – 10.0]) and women (4.2% [95% CI, 0.2 – 8.3]) there was a significant increase in the AAPC rates for drug poisoning deaths involving antidepressants with no change points observed (Tables 1 & Table 2). Although the age-standardised rate for women in 2017 (1.40 per 100,000) was lower than the rate in 2004 (1.71 per 100,000), the yearly rates fluctuated during the reported period with an overall upward trend. This did not result in any significant change points.

Antidepressants were the only drug group in which a positive relationship between prescription data and drug poisoning data was observed for both men (β = 0.004, [95% CI -0.003, 0.022], p < 0.05) and women (β = 0.006, [95% CI 0.000, 0.012], p < 0.05) (Figure 3).

Insert Figure 3

### *Alcohol*

Analysis showed that the rate of women who died of drug poisoning deaths involving alcohol decreased with an AAPC decrease of 4.0% (95% CI, -5.8 – -2.1) between 2004 and 2017 (Table 2). There was no statistically significant AAPC in rates for men in the same period (Table 1). No significant change points were observed for men or women.

### *Cocaine*

Drug poisoning deaths involving cocaine appear to fluctuate over time. An accelerated increase during the periods 2004 to 2006 and 2010 to 2017 with a significant decrease during the intervening period, 2006 to 2010 was observed among men, with an AAPC increase of

7.7% (95% CI, 2.2 – 13.6) (Table 1). Accelerated increases were also identified among women in the periods 2004 to 2008 and 2011 to 2017, however no significant AAPC was observed among women (Table 2).

### *Heroin*

No change, for either sex, was observed for deaths involving heroin over the study period (Tables 1 & Table 2). Although not statistically significant, for men there was a high APC for poisoning deaths involving heroin between 2004 and 2006, followed by a decrease, albeit not significant, from 2006 to 2017.

## Discussion

### *Summary of findings*

This repeated cross-sectional study found that there has been no significant reduction in overall drug poisoning deaths in Ireland during the period 2004 to 2017. The ASR for drug poisoning deaths increased among men, albeit in the early years of the study, with no significant change in the latter stage of the study period. The ASR for overall drug poisoning deaths among women remained stable.

A similar pattern was found among men when CNS depressant drugs were implicated in poisoning deaths, with a significant increase noted only for earlier years. In contrast, a significant increase was found in the most recent time period for deaths among women involving CNS depressant drugs.

The increasing trend for two or more CNS depressant drugs implicated in drug poisoning deaths, especially the more recent significant increase among women, is of concern. This finding suggests that CNS depressant drugs may be impacting more on polydrug poisoning deaths, albeit in more recent years, among women relative to men.

Our study findings differ from that reported in the U.S. where prescription opioids and more recently fentanyl, are the main drugs driving the increase in drug poisoning deaths (2). In Ireland, while drug poisoning deaths involving prescription opioids have increased, deaths involving fentanyl remain low (22). It is cocaine, antidepressants and benzodiazepines; especially when combined with other CNS depressant drugs, that are the drugs with the highest increasing trend in drug poisoning deaths in Ireland.

Our previous research has shown a stronger association of methadone being present as part of a combination of CNS depressant drugs in drug poisoning deaths among women relative to men (28). This study found that the majority of deaths involving prescription opioids related to methadone (both prescribed and illicit), with women disproportionately affected. Although fewer women receive OAT in Ireland (29) and Europe (9), a higher percentage of women relative to men, who died of a drug poisoning death involving methadone, were registered for OAT at the time of their death. A growing body of evidence suggests that mortality risk during OAT is time varying (30). As a full opioid agonist, methadone can cause hazardous respiratory depression and is associated with an elevated risk of drug poisoning during the first four weeks of treatment initiation (30-33). The risk of drug poisoning mortality immediately following OAT dropout, particularly the first four weeks is also high (32-35). Given, that clients' treatment status on the CTL remains active for up to four weeks from their first day of non-attendance with their treatment provider, it is plausible that some clients recorded as experiencing a drug poisoning death in treatment had in-fact left treatment.

Notwithstanding the fact that deaths involved prescribed methadone, the lack of a relationship between the rate of prescription opioids dispensed, which mainly consisted of methadone, and the rate of drug poisoning deaths involving prescription opioids, which also mainly involved methadone, among men adds to the evidence that OAT protects against

drug-related deaths (35, 36). The fact that this relationship, although weak, is positive for women, may indicate the need for increased awareness among prescribers and people who use drugs of the differences between men and women in drug metabolism and drug action, and the risks associated with both prescribing and consuming multiple CNS depressant drugs.

Benzodiazepines were the most frequently found drug group in poisoning deaths involving two or more CNS depressant drugs, therefore the combination of benzodiazepines with other CNS depressant drugs warrants further investigation. Polydrug use has been recognised as an area of public health concern and has been described as "the norm" among people who use drugs (37). Polydrug use, especially opioids with sedative drugs, including benzodiazepines, have been associated with active post-traumatic stress disorder (38) and with serious health risks including drug poisoning deaths (39).

This study found that drug poisoning deaths involving prescription opioids, benzodiazepines and/or antidepressants had the greatest increase among women during the study period. This result contributes to a growing body of research highlighting opioids, benzodiazepines and antidepressants as the main drugs involved in drug poisoning deaths among women (11). While acknowledging the increased availability of illicit ('street') drugs especially benzodiazepines and prescription opioids, these drugs are prescription drugs therefore increased monitoring of prescribing practises in addition to enabling and enforcing use of electronic prescriptions, is required. Facilitation linkage of NDRDI data to dispensed prescription data would assist in confirming whether the drug involved in drug poisoning deaths was prescribed to the individual or if it was obtained illicitly. This information is not always recorded in coronial files.

Our study showed a significant association, for both sexes, between the rate of antidepressants dispensed and the rate of poisoning deaths involving antidepressants and

while this does not indicate causality it does suggest a relationship. Men are known to have higher rates of mental health disorders relative to women, however conditions such as anxiety and depression are reported to be higher among women, which may be as a result of reporting bias among men who tend to mask their symptoms more than women (40). Taking this into consideration, the higher rates of dispensing of antidepressants among men may be an indirect indicator of more men seeking medical help for mental health issues. This increase in dispensing correlates with results from a population prevalence study which showed an increasing trend in use of antidepressants among both men and women (41). Further research into the type of antidepressants, both dispensed and implicated in drug poisoning deaths, as well as their impact on suicide deaths by poisoning is necessary.

Per capita consumption of alcohol has been shown to be an important determinant of alcohol-related deaths which include poisoning deaths (42). Per capita consumption of alcohol in Ireland decreased during the study period (43), in line with our results which show a decrease in drug poisoning deaths involving alcohol over the same period, with a significant decrease noted for women. This is welcoming and may indicate a relationship between decreased consumption and decreased alcohol poisoning deaths thus strengthens the need for full implementation of the Public Health (Alcohol) Bill 2018 (44) in Ireland. Of note, as alcohol is a CNS depressant, prescribers should assess for and advise on alcohol use when prescribing CNS depressant drugs.

Following an increase in the early years of the study period, rates of drug poisoning deaths involving cocaine decreased for men and women at a time of economic recession in Ireland (45). Our findings show that as the economy improved post-recession, there was a significant increase in cocaine-related drug poisoning deaths for both sexes, similar to that seen in other jurisdictions (46) with the increase more substantial among women. Results from a national prevalence study during the study period also showed that while there was an increase in

recent (last month) use of cocaine among men, there was a significant increase in recent use of cocaine among women (41). Of interest, in recent years there has been an increase in people seeking treatment related to cocaine use (9), with an increase in the proportion of women in receipt of treatment for cocaine during the latter years of the study (47). This trend highlights the impact of market forces on drug poisoning deaths and reflects the need to extend education and treatment related to cocaine use, especially for women.

### *Clinical and policy implications*

The increasing trend of CNS depressant drugs involved in drug poisoning deaths may indicate both an overreliance on these types of drugs to treat or cope with both addiction and other mental health issues, in addition to inappropriate, including illicit use of these drugs by individuals in the community.

Increasing awareness in both the treatment settings and in the community, of the synergistic effect of taking multiple CNS depressant drugs, including alcohol, is warranted. This should include engagement with advocacy groups who work with people who use drugs, to promote the dissemination of information to harder to reach groups including those who are homeless. In addition, increased awareness among medical practitioners of the physiological sex differences affecting drug activity, when prescribing CNS depressants is important. These differences include; slower renal clearance of certain CNS depressant drugs, including pregabalin; women being more sensitive to and experience enhanced effectiveness of opioids; and benzodiazepines having a longer duration of action for women (14, 15).

The significant increase in deaths involving benzodiazepines in both men and women is of concern. The decreasing rate of benzodiazepines dispensed through the GMS/PCRS system corresponds to changes in policy, which introduced stricter prescribing regulations (48, 49), making a positive impact on prescribing practices. However given the increase in illicit

benzodiazepines in the community, as indicated by the increase in seizure data, and reports from experts in the area (50, 51) tighter controls on prescribing benzodiazepines may have partially resulted in an increased use of illicit benzodiazepines. These illicit benzodiazepines have higher potency and are available at low cost (52). Due to the shorter half-life of illicit benzodiazepines, people who use these drugs tend to take repeated dosages which increases the risk of a poisoning death.

In Ireland, there were no national guidelines for benzodiazepine maintenance treatment, however in response to the COVID-19 pandemic; given the high rate of benzodiazepine misuse among people on OAT, benzodiazepine maintenance treatment was offered to all clients on OAT with established benzodiazepine dependency (53). In 2019, 10% of people in Ireland in receipt of treatment for drug use, reported benzodiazepines as their primary problem while 35% reported benzodiazepines as an additional problem drug (47). Given the increasing risk of drug poisoning deaths involving benzodiazepines, continuation of and improved access to; maintenance treatment along with guidelines, and detoxification for people who are known to be misusing or dependent on benzodiazepines should be considered. Research has shown that brief interventions delivered in the primary care setting are a very effective method of both reducing and discontinuing long term benzodiazepine use (54).

While it is disappointing to see no significant decrease in deaths involving heroin, the stabilisation of rates for drug poisoning deaths involving heroin may be due to increased access to treatment, and/or it may reflect drug markets or drug use patterns among the population. Of note, prevalence data also indicate a stabilisation in the use of heroin in the population (41). It is known that between 2010 and 2011 there was a severe shortage of heroin in the European market (55) the reasons for which were multifaceted. In Ireland, the heroin drought was reflected in a decrease in heroin poisoning deaths in 2011, but this

decrease was counterbalanced by an increase in drug poisoning deaths involving benzodiazepines and methadone (22). The heroin drought may be an example of how despite the lack of heroin, the underlying problem of drug addiction did not dissipate. Drug markets influence changing patterns in drug use; with a decrease in availability of heroin, people who used heroin may have had no alternative but to revert to using other illicit (street) drugs.

There has been a decrease in recent years in the number of new treatment entries for OAT (9, 47). Seizures of heroin in the European Union had stabilised since 2011, however data from 2018 shows a significant increase in seizures involving heroin (9). This, in combination with recent evidence from Australia showing an increase in deaths involving heroin (56), indicates that heroin remains a main contributor to drug-related harm including drug poisoning deaths worldwide.

Although beyond the scope of this study, it would be of interest to assess the impact of the codeine dispensing guidelines introduced in 2010, to ensure the safe dispensing of non-prescription products containing codeine (57), may have had on drug poisoning deaths involving opioids.

In an effort to prevent drug poisoning deaths among both men and women, a combination of pharmacological, psychosocial and harm reduction interventions, with increasing access to sex-specific and age appropriate treatment and wider availability of naloxone, should be implemented (58-60). Promoting more open communication between prescribers and clients should enhance provision of appropriate treatment and help clients make informed decisions about their drug use. Innovative models of virtual healthcare delivery, such as those adapted during the COVID-19 pandemic, could also help minimise barriers to accessing services and consideration should be given to incorporating this model of care, in addition to face to face consultations in future delivery of care (61). In addition services tailored to the particular

needs of women are required, such as increasing the number of residential beds with childcare facilities.

Advocates for people who use drugs should be consulted on and contribute to policy decisions around reducing harms associated with drug use. Policies to reduce drug poisoning deaths should move from a criminal justice focus to a more public health focus (62, 63). Harm reduction initiatives along with treatment interventions, which include pharmaceutical combined with psychosocial assistance, need to focus on the range of problematic drugs. Furthermore, reducing stigma associated with drug use and drug poisoning deaths, aligned with actions to target economic deprivation, are required.

Future research in the area of drug poisoning deaths should include stratification by sex. Sex-specific evidence is required to support appropriate policy actions to reduce drug poisoning deaths.

## Strengths and limitations

The main strength of this study is the use of national data validated from a number of sources, ensuring accuracy and completeness of data available to examine trends in drug poisoning deaths by sex. Access to prescription data for prescribed opioids, benzodiazepines and antidepressants enabled assessment of the relationship between trends in prescribing for and drug poisoning death rates involving these drugs.

Given the complexities involved in death investigations it may be 12 to 18 months after death before completion of an inquest, and data becomes available for the NDRDI, which limits the emergence of any recent trends. However given that the observation period of 2004 to 2017 was used in this study this strengthens the completeness of the data.

Limitations of this study include the reliance on individual Coroners to implicate drugs in poisoning deaths, which can be challenging when multiple drugs are present on a toxicology report. Information on whether the drugs were prescribed to the individual is frequently not available in coronial files which limits the assessment of illicit use of these drugs and the impact of illicit drugs on these deaths.

Lack of data on private prescription drugs dispensed stratified by sex, limits analysis to those dispensed through the GMS/PCRS scheme and so analysis does not include private prescriptions. Also, the GMS/PCRS scheme over-represents the more socially deprived and older aged populations, and therefore, does not represent the total population use of these drugs. Also, the lack of data on consumption of other drugs, including alcohol, cocaine and heroin, stratified by sex, limited the analysis on these drugs.

Data on individuals in receipt of OAT was limited to aggregated data giving the total number including breakdown by sex but not by age group, therefore crude rate of prescription opioids, not age-standardised rates, was calculated for this data. Methadone is a prescribed opioid and therefore was included in this drug group, however results shows that the majority of methadone implicated in these drug poisoning deaths was not prescribed to the individual and thus was illicit methadone.

## Conclusion

There is a need for an efficient healthcare response to polydrug use, which should include pragmatic harm reduction information around potentially lethal combinations of drugs, including alcohol, and how to reduce consumption of multiple drugs, especially CNS depressant drugs. In addition to endorsement of a nationwide ePrescription system, an active prescription monitoring system would assist in increased pharmacovigilance, especially with prescribing of multiple CNS depressant drugs, in particular among women; due physiological

sex differences affecting drug activity, and among people with a history of problematic drug use including alcohol.

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## Declaration of Competing interest

No conflict declared.

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## Author contributions

Ena Lynn, Professor Kathleen Bennett and Dr Gráinne Cousins designed the study. Ena Lynn was responsible for the writing of the manuscript and undertook the statistical analysis with guidance from Professor Kathleen Bennett and Dr Grainne Cousins. All authors provided critical input to drafts of the paper. All authors contributed to the interpretation of the data and approved the final manuscript.

## References


1. Shiels M S, Tatalovich Z, Chen Y, et al. Trends in Mortality From Drug poisonings, Suicide, and Alcohol-Induced Deaths in the United States From 2000 to 2017. *JAMA Netw Open,* 2020;**3**:e2016217. https://doi.org/10.1001/jamanetworkopen.2020.16217

2. Scholl L, Seth P, Kariisa M, et al. Drug and Opioid-Involved Overdose Deaths - United States, 2013-2017. *MMWR: Morb Mortal Wkly Rep,* 2019;67:1419-1427. https://doi.org/10.15585/mmwr.mm675152e1

3. Seth P, Scholl L, Rudd R. A, et al. Overdose Deaths Involving Opioids, Cocaine, and Psychostimulants - United States, 2015-2016. *Morb Mortal Wkly Rep,* 2018;**67**:349-358. https://doi.org/10.15585/mmwr.mm6712a1

4. McCall Jones C, Baldwi, G. T & Compton W M. Recent Increases in Cocaine-Related Overdose Deaths and the Role of Opioids. *American Journal of Public Health,* 2017;**107**:430-432. https://doi.org/10.2105/AJPH.2016.303627

5. Best A F, Haozous E A, Berrington de Gonzalez A, et al. Premature mortality projections in the USA through 2030: a modelling study. *Lancet Public Health,* 2018;**3**:e374-e384. https://doi.org/10.1016/S2468-2667(18)30114-2

6. Man N, Chrzanowska A, Dobbins T, et al. Trends in drug-induced deaths in Australia, 1997-2018. Drug Trends Bulletin Series. Sydney: National Drug and Alcohol Research Centre. 2019. https://ndarc.med.unsw.edu.au/resource/trends-drug-induced-deaths-australia-1997-2018 (accessed Sept 2020)

7. Kimber J, Hickman M, Strang J, et al. Rising opioid-related deaths in England and Scotland must be recognised as a public health crisis. *Lancet Psychiatry,* 2019;**6**:639-640. https://doi.org/10.1016/S2215-0366(19)30209-3

8. EMCDDA. European Drug Report 2014: Trends and Developments. 2014 https://www.emcdda.europa.eu/publications/edr/trends-developments/2014_en (assessed Oct 2020)

9. EMCDDA. European Drug Report 2020: Trends and Developments. 2020. https://www.emcdda.europa.eu/publications/edr/trends-developments/2020_en (assessed 25 Sept 2020)

10. Jalal H, Buchanich J M, Roberts M S et al. Changing dynamics of the drug overdose epidemic in the United States from 1979 through 2016. *Science,* 2018;**361**:6408. https://doi.org/10.1126/science.aau1184

11. Lynn E, Doyle A, Keane M, et al. Drug poisoning deaths among women: a scoping review. *J Stud Alcohol Drugs,* 2020;**81**:543-555. https://doi.org/10.15288/jsad.2020.81.543

12. Tweed E, Miller R, Mathesone C. Why are drug-related deaths among women increasing in Scotland? A scoping of possible explanations. Edinburgh: Scottish Government. 2018 http://www.gov.scot/publications/drug-related-deaths-women-increasing-scotland-9781787810129/(assessed Sept 2020)

13. Centers for Disease Control and Prevention. Prescription Painkiller Overdoses: A Growing Epidemic, Especially Among Women. 2013. https://www.cdc.gov/vitalsigns/prescriptionpainkilleroverdoses/index.html (assessed 7 March 2020)

14. Algren D A, Monteilh C P, Punja M, et al. Fentanyl-associated fatalities among illicit drug users in Wayne County, Michigan (July 2005-May 2006). *Journal of Medical Toxicology,* 2013;**9**:106-115. https://doi.org/10.1007/s13181-012-0285-4

15. Whitley H, Lindsey W. Sex-based differences in drug activity. *Am Fam Physician,* 2009;**80**:1254-1258. https://doi.org/10.1016/S0140-6736(19)31812-4

16. VanHouten J P, Rudd R A, Ballesteros M F, et al. Drug Overdose Deaths Among Women Aged 30-64 Years - United States, 1999-2017. *MMWR: Morb Mortal Wkly Rep,* 2019;**68**:1-5. https://doi.org/10.15585/mmwr.mm6801a1

17. Tyrrell E G, Orton E, Sayal K, et al. Differing patterns in intentional and unintentional poisonings among young people in England, 1998–2014: a population-based cohort study. *J Public Health (Oxf),* 2017;**39**:e1-e9. https://doi.org/10.1093/pubmed/fdw075

18. STROBE Statement. STROBE Statement. https://www.strobe-statement.org/fileadmin/Strobe/uploads/checklists/STROBE_checklist_v4_combined.pdf (assessed 30 May 2019)

19. Lynn E, Lyons S, Walsh S, et al. Trends in deaths among drug users in Ireland from traumatic and medical causes, 1998 to 2005. 2019 Dublin: Health Research Board. https://www.drugsandalcohol.ie/12775/ (assessed Sept 2020)

20. EMCDDA. Drug-Related Deaths (DRD) Standard Protocol, version 3.2. Lisbon: EMCDDA. 2010 https://www.emcdda.europa.eu/html.cfm/index107404EN.html_en (assessed Sept 2020)

21. Roxburgh A, Pilgrim J L, Hall W D, et al. Accurate identification of opioid overdose deaths using coronial data. *Forensic Sci Int,* 2018;**287**:40-46. https://doi.org/10.1016/j.forsciint.2018.03.032

22. Health Research Board. National Drug-Related Deaths Index 2008 to 2017 data. Dublin: Health Research Board. 2019 https://www.drugsandalcohol.ie/31275 (assessed Oct 2020)

23. Sinnott S J, Bennett K, Cahir C. Pharmacoepidemiology resources in Ireland-an introduction to pharmacy claims data. *Eur J Clin Pharmacol,* 2017;**73**:1449-1455. https://doi.org/10.1007/s00228-017-2310-7

24. Central Statistics Office. StatBank Annual Population Estimates. 2020. https://statbank.cso.ie/px/pxeirestat/Statire/SelectVarVal/Define.asp?maintable=PEA01&PLanguage=0 (assessed 15 Feb 2020)

25. Health Service Executive. Primary Care Reimbursement Service: Statistical Analysis of Claims and Payments 2008 to 2017. 2017. https://www.sspcrs.ie/portal/annual-reporting/report/annual (assessed 12 Sept 2020)

26. Eurostat. Revision of the European Standard Population – Report of Eurostat's Task Force. Luxembourg: European Commission. 2013 https://doi.org/10.2785/11470 (assessed Feb 2020)

27. National Cancer Institute. Joinpoint trend analysis softward. 2020 https://surveillance.cancer.gov/joinpoint/ (assessed 4 Aug 2020)

28. Lynn E, Cousins G, Lyons S, et al. A repeated cross-sectional study of factors associated with pregabalin-positive poisoning deaths in Ireland.

*Drug Alcohol Depend,* 2020;**206**:107741. https://doi.org/10.1016/j.drugalcdep.2019.107741

29. Cousins G, Boland F, Barry J, et al. J-shaped relationship between supervised methadone consumption and retention in methadone maintenance treatment (MMT) in primary care: National cohort study. *Drug Alcohol Depend,* 2017;**173**: 126-131. https://doi.org/10.1016/j.drugalcdep.2016.12.009

30. Sordo L, Barrio G, Bravo M J, et al. Mortality risk during and after opioid substitution treatment: systematic review and meta-analysis of cohort studies. *Br Med J*, 2017;**357**: j1550. https://doi.org/10.1136/bmj.j1550

31. Cousins G, Teljeur C, Motterlini N, et al. Risk of drug-related mortality during periods of transition in methadone maintenance treatment: A cohort study. *J Subst Abuse Treat,* 2011;**41**:252-260. https://doi.org/10.1016/j.jsat.2011.05.001

32. Durand L, O'Driscoll D, Boland F, et al. Do interruptions to the continuity of methadone maintenance treatment in specialist addiction settings increase the risk of drug-related poisoning deaths? A retrospective cohort study. *Addiction*. 2020;**115**:1867-1877. https://doi.org/10.1111/add.15004

33. Evans E, Li L, Min J, et al. Mortality among individuals accessing pharmacological treatment for opioid dependence in California, 2006-10. *Addiction,* 2015;**110**:996-1005. https://doi.org/10.1111/add.12863

34. Kimber J, Larney S, Hickman M, et al. Mortality risk of opioid substitution therapy with methadone versus buprenorphine: a retrospective cohort study. *Lancet Psychiatry*, 2015;**2**:901-908. https://doi.org/10.1016/s2215-0366(15)00366-1

35. Cousins G, Boland F, Courtney B, et al. Risk of mortality on and off methadone substitution treatment in primary care: a national cohort study. *Addiction,* 2016;**111**:73-82. https://doi.org/10.1111/add.13087

36. Degenhardt L, Randall D, Hall W, et al. Mortality among clients of a state-wide opioid pharmacotherapy program over 20 years: risk factors and lives saved. *Drug Alcohol Depend,* 2009;**105**:9-15. https://doi.org/10.1016/j.drugalcdep.2009.05.021

37. Jarlenski M, Barry C L, Gollust S, et al. Polysubstance Use Among US Women of Reproductive Age Who Use Opioids for Nonmedical Reasons. *Am J Public Health,* 2017;**107**:1308-1310. https://doi.org/10.2105/AJPH.2017.303825

38. Hassan A, Le Foll B. Polydrug use disorders in individuals with opioid use disorder. *Drug Alcohol Depend,* 2019;**198**:28-33. https://doi.org/10.1016/j.drugalcdep.2019.01.031

39. Calcaterra S, Glanz J, Binswanger I. National trends in pharmaceutical opioid related overdose deaths compared to other substance related overdose deaths: 1999–2009. *Drug Alcohol Depend,* 2013;**131**:263-270. https://doi.org/10.1016/j.drugalcdep.2012.11.018

40. Affleck W, Carmichael V, Whitley R. Men's Mental Health: Social Determinants and Implications for Services. *Can J Psychiatry.* 2018;**63**:581-589. https://doi.org/10.1177/0706743718762388

41. National Advisory Committee on Drugs and Alcohol, Northern Ireland. Department of Health. Prevalence of drug use and gambling in Ireland & drug use in Northern Ireland. Bulletin 1. Dublin: National Advisory Committee on Drugs and Alcohol. 2016. https://www.drugsandalcohol.ie/26364/(assessed Oct 2020)

42. Norström T, Mäkelä,P. The connection between per capita alcohol consumption and alcohol-specific mortality accounting for unrecorded alcohol consumption: The case of Finland 1975–2015. *Drug Alcohol Rev*, 2019;**38**:731-736. https://doi.org/10.1111/dar.12983

43. Office of Revenue Commissioners. Excise Receipts by Commodity. 2020. https://www.revenue.ie/en/corporate/information-about-revenue/statistics/excise/receipts-volume-and-price/excise-receipts-commodity.aspx (assessed 4 July 2020)

44. Government of Ireland. Public Health (Alcohol) Act 2018. 2018. http://www.irishstatutebook.ie/eli/2018/act/24/enacted/en/html (assessed 14 Sept 2020)

45. Eurostat. General government deficit/surplus: % of GDP and million EUR. 2020.https://ec.europa.eu/eurostat/databrowser/view/tec00127/default/table?lang=en (assessed 23 Sept 2020)

46. Hedegaard H, Spencer M R, Garnett M F. Increase in drug overdose deaths involving cocaine: United States, 2009–2018. NCHS Data Brief No.384. Centre for Disease Control and Prevention. 2020. https://www.cdc.gov/nchs/data/databriefs/db384-H.pdf (assessed Oct 2020)

47. O'Neill D, Carew A, Lyons S. Drug Treatment in Ireland 2013 to 2019. Dublin: Health Research Board. 2020. https://www.drugsandalcohol.ie/32094 (assessed 19 Sept 2020)

48. Benzodiazepine Committee. Benzodiazepines: good practice guidelines for clinicians. Dublin: Department of Health and Children. 2002. https://www.drugsandalcohol.ie/5349/(assessed 27 Sept 2020)

49. Department of Health. Commencement of the Misuse of Drugs (Amendment) Act 2016 and associated Ministerial Regulations and Orders. Dublin. 2017. http://www.health.gov.ie/blog/publications/commencement-of-the-misuse-of-drugs-amendment-act-2016-and-associated-ministerial-regulations-and-orders/(assessed Oct 2020)

50. Duffin T, Keane M, Millar S R. Street tablet use in Ireland. A Trendspotter study on use, markets, and harms. Dublin: Ana Liffey Drug Project. 2020. https://www.drugsandalcohol.ie/31872/(assessed Oct 2020)

51. EMCDDA. PERSPECTIVES ON DRUGS:The misuse of benzodiazepines among high-risk opioid users in Europe. 2018. https://www.emcdda.europa.eu/topics/pods/benzodiazepines_en (assessed 27 Sept 2020)

52. Ryan V. 'Fake' benzos potency fears rise. *Irish Medical Times*. Dublin. 2020. https://www.imt.ie/news/fake-benzos-potency-fears-rise-31-08-2020/(assessed 31 Aug 2020)

53. O'Carroll A, Duffin T, Collins J. Harm reduction in the time of COVID-19: Case study of homelessness and drug use in Dublin, Ireland. *Int J Drug Policy,* 2021;**87**:102966. http://doi.org/10.1016/j.drugpo.2020.102966

54. Lynch T, Ryan C, Hughes C M, et al. Brief interventions targeting long-term benzodiazepine and Z-drug use in primary care: a systematic review and meta-analysis. *Addiction,* 2020;**115**:1618-1639. https://doi.org/10.1111/add.14981

55. EMCDDA. Trendspotter Summary Report Recent Shocks in the European Heroin Market: Explanations and Ramifications In. Lisbon: EMCDDA. 2011. https://www.emcdda.europa.eu/scientific-studies/2011/trendspotters-report_en (assessed Oct 2020)

56. Australian Institute of Health and Welfare. Alcohol, tobacco & other drugs in Australia. 2020. https://www.aihw.gov.au/reports/phe/221/alcohol-tobacco-other-drugs-australia/contents/drug-types/illicit-opioids-heroin (assessed 3 Sept 2020)

57. The Pharmaceutical Society of Ireland. Non-prescription medicinal products containing codeine: Guidance for pharmacists on safe supply to patients. Dublin: The Pharmaceutical Society of Ireland. 2010. www.drugsandalcohol.ie/13191 (assessed 6 Oct 2020)

58. Fairbairn N, Coffin P O, Walley A Y. Naloxone for heroin, prescription opioid, and illicitly made fentanyl overdoses: Challenges and innovations responding to a dynamic epidemic. *Int J Drug Policy,* 2017;**46**:172-179. https://doi.org/10.1016/j.drugpo.2017.06.005

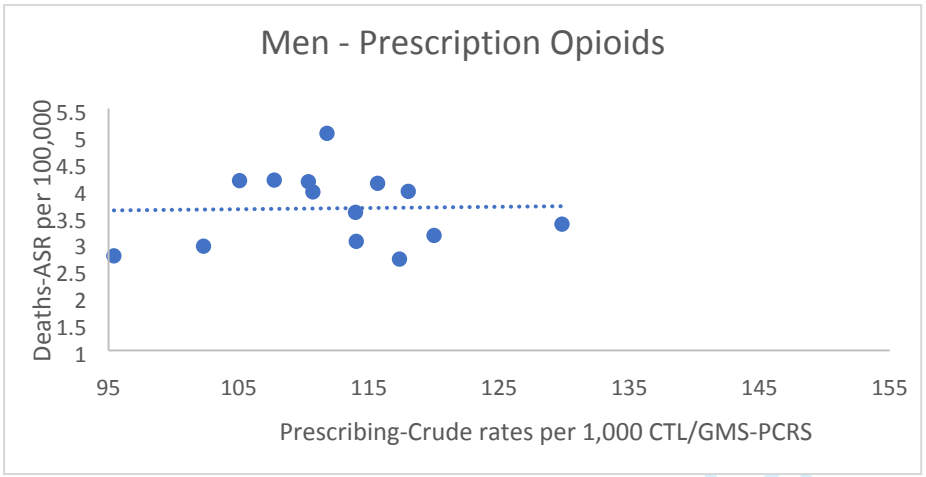
59. Degenhardt L, Grebely J, Stone J, et al. Global patterns of opioid use and dependence: harms to populations, interventions, and future action. *Lancet,* 2019;**394**:1560-1579. https://doi.org/10.1016/S0140-6736(19)32229-9

60. WHO/UNODC. International standards for the treatment of drug use disorders: revised edition incorporating results of field-testing. Geneva: World Health Organization and United Nations Office on Drugs and Crime. 2020. https://www.who.int/publications/i/item/international-standards-for-the-treatment-of-drug-use-disorders

61. Crowley D, Delargy I. A national model of remote care for assessing and providing opioid agonist treatment during the COVID-19 pandemic: a report. *Harm Reduct J,* 2020;**17**:49. https://doi.org/10.1186/s12954-020-00394-z

62. EMCDDA. Health and social responses to drug problems: a European guide. 2017. https://www.emcdda.europa.eu/publications/manuals/health-and-social-responses-to-drug-problems-a-european-guide_en (assessed 20 Sept 2020)

63. UNODC. Treatment and Care of people with Drug Use Disorders in Contact with the Criminal Justice System: Alternatives to Conviction or Punishment. 2016.https://www.unodc.org/unodc/en/drug-prevention-and-treatment/treatment-and-care-of-people-with-drug-use-disorders-in-contact-with-the-criminal-justice-system_-alternatives-to-conviction-or-punishment.html (assessed Oct 2020)



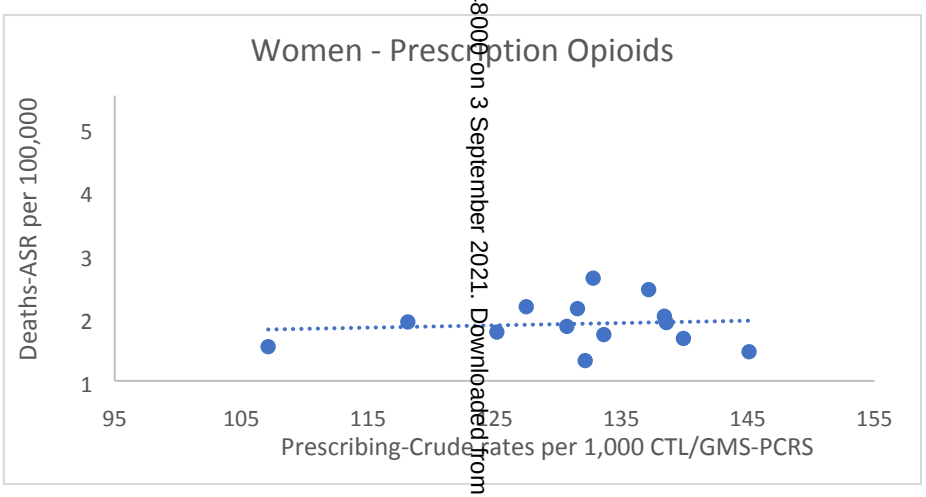
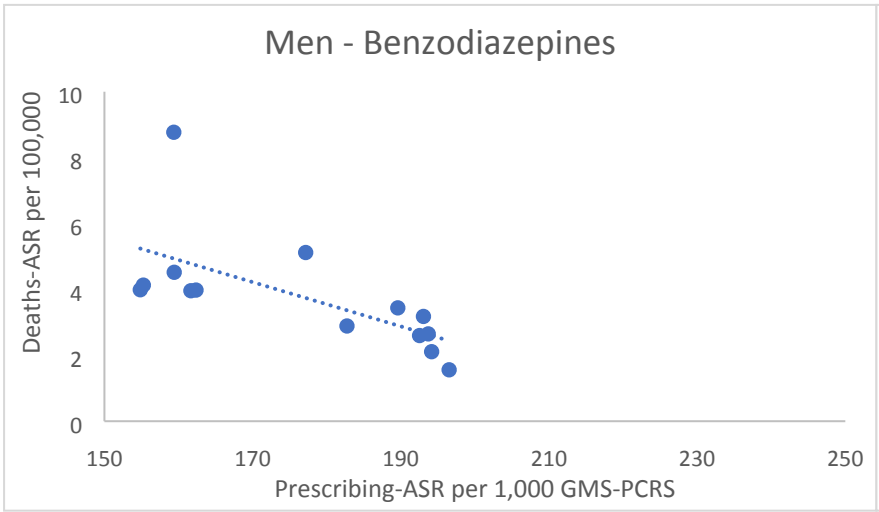




Figure 1. Prescription Opioids: Age-standardised rates per 100,000 of drug poisoning deaths involving prescription opioids and crude rates per 1,000 of individuals in receipt of prescribed opioids through the CTL and GMR/PCRS; 2004 to 2017.



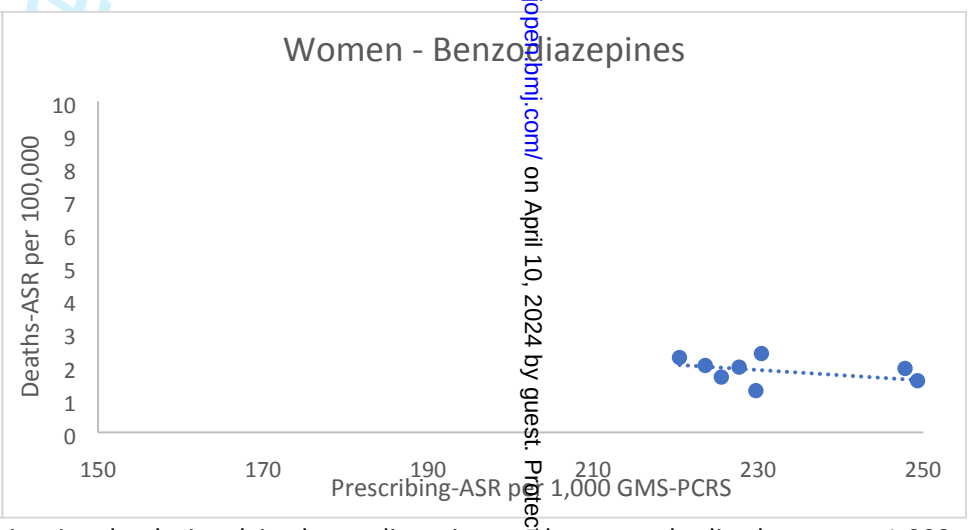




Figure 2. Benzodiazepines: Age-standardised rates per 100,000 of drug poisoning deaths involving benzodiazepines and age-standardised rates per 1,000 of individuals in receipt of prescribed benzodiazepines through the GMR/PCRS; 2004 to 2017.

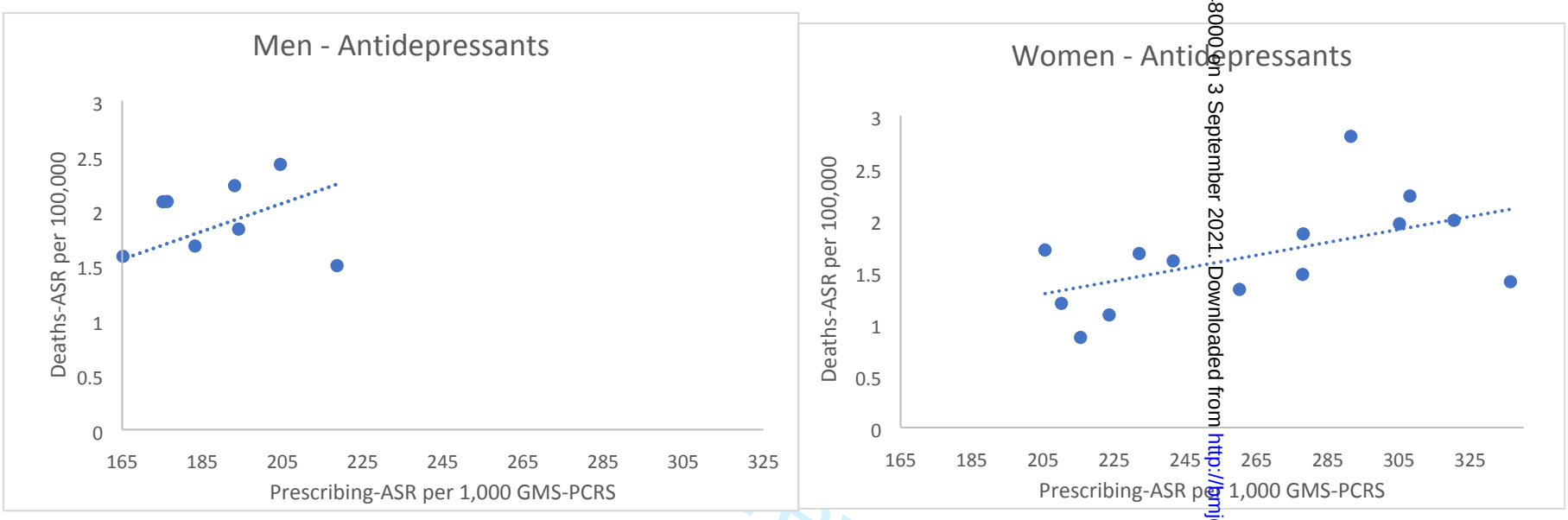



Figure 3. Antidepressants: Age-standardised rates per 100,000 of drug poisoning deaths involving antidepressants and age-standardised rates per 1,000 of individuals in receipt of prescribed antidepressants through the GMR/PCRS; 2004 to 2017.

**STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional studies***

| Section/Topic | Item # | Recommendation | Reported on page # |
|---|---|---|---|
| **Title and abstract** | 1 | (*a*) Indicate the study's design with a commonly used term in the title or the abstract | 1 |
| | | (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found | 2 |
| **Introduction** | | | |
| Background/rationale | 2 | Explain the scientific background and rationale for the investigation being reported | 5 |
| Objectives | 3 | State specific objectives, including any prespecified hypotheses | 6 |
| **Methods** | | | |
| Study design | 4 | Present key elements of study design early in the paper | 6 |
| Setting | 5 | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection | 7 |
| Participants | 6 | (*a*) Give the eligibility criteria, and the sources and methods of selection of participants | 7-10 |
| Variables | 7 | Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable | 6 |
| Data sources/ measurement | 8* | For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group | 7-9 |
| Bias | 9 | Describe any efforts to address potential sources of bias | |
| Study size | 10 | Explain how the study size was arrived at | |
| Quantitative variables | 11 | Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why | 9-11 |
| Statistical methods | 12 | (*a*) Describe all statistical methods, including those used to control for confounding | 9-11 |
| | | (*b*) Describe any methods used to examine subgroups and interactions | 9-11 |
| | | (*c*) Explain how missing data were addressed | |
| | | (*d*) If applicable, describe analytical methods taking account of sampling strategy | |
| | | (*e*) Describe any sensitivity analyses | |
| **Results** | | | 11 |

| | | | |
|---|---|---|---|
| Participants | 13* | (a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed | 11 |
| | | (b) Give reasons for non-participation at each stage | |
| | | (c) Consider use of a flow diagram | |
| Descriptive data | 14* | (a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders | 11-14 |
| | | (b) Indicate number of participants with missing data for each variable of interest | |
| Outcome data | 15* | Report numbers of outcome events or summary measures | 11-14 |
| Main results | 16 | (*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included | 11-17 |
| | | (*b*) Report category boundaries when continuous variables were categorized | |
| | | (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period | |
| Other analyses | 17 | Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses | 11-17 |
| **Discussion** | | | |
| Key results | 18 | Summarise key results with reference to study objectives | 17-18 |
| Limitations | 19 | Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias | 24-25 |
| Interpretation | 20 | Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence | 17-23 |
| Generalisability | 21 | Discuss the generalisability (external validity) of the study results | 18-23 |
| **Other information** | | | |
| Funding | 22 | Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based | 26 |

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

# Trends in drug poisoning deaths, by sex, in Ireland: a repeated cross-sectional study from 2004 to 2017

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# Trends in drug poisoning deaths, by sex, in Ireland: a repeated cross-sectional study from 2004 to 2017

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# Trends in drug poisoning deaths, by sex, in Ireland: a repeated cross-sectional study from 2004 to 2017


## Abstract

**Objective** Examine sex differences in age-standardised rates (ASR) of overall and drug-specific drug poisoning deaths, in Ireland between 2004 and 2017.

**Design** Repeated cross-sectional study.

**Setting** Drug poisoning deaths in Ireland.

**Participants** National Drug-Related Deaths Index (NDRDI) and pharmacy claims database (PCRS/GMS) data, 2004 to 2017.

**Outcome measures** Primary outcome: trends in drug poisoning death rates by sex. Secondary outcomes: trends in drug poisoning death rates involving (1) any CNS depressants (2) ≥ 2 CNS depressants, and (3) individual drug classes (e.g. prescription opioids, benzodiazepines, antidepressants, alcohol, cocaine, and heroin) by sex. Joinpoint Regression was used to examine trends, stratified by sex, in the ASR of drug poisoning deaths (2004 to 2017), change points over time and average annual percentage changes (AAPCs) with 95% confidence intervals (CI).

**Results** Increased ASR for all drug poisoning deaths from 6.86 (95% CI 6.01-7.72) per 100,000 in 2004 to 8.08 (95% CI 7.25-8.91) per 100,000 in 2017 was mainly driven by increasing deaths among men (AAPC 2.6% [95% CI, 0.2 - 5.1]) with no significant change observed among women. Deaths involving ≥ 2 CNS depressants increased for both men (AAPC 5.6% [95% CI, 2.4 - 8.8]) and women (AAPC 4.0% [95% CI, 1.1 - 6.9]). Drugs with the highest significant AAPC increases for men were cocaine (7.7% [(95% CI, 2.2 - 13.6]), benzodiazepines (7.2% [(95% CI, 2.9 - 11.6]), antidepressants (6.1% [(95% CI, 2.4 - 10.0]),

and prescription opioids (3.5% [(95% CI, 1.6 - 5.5]). For women, the highest AAPC was for antidepressants (4.2% [(95% CI, 0.2 - 8.3]), benzodiazepines (3.3% [(95% CI, 0.1 - 6.5]), and prescription opioids (3.0% [(95% CI, 0.7 - 5.3]).

**Conclusion** Drugs implicated in drug poisoning deaths vary by sex. Policy response should include prescription monitoring programmes, and practical harm reduction information on polydrug use, especially CNS depressant drugs.

**Key words** Drug; poisoning; death; men; women; sex; gender

## Article Summary

### *Strengths and limitation of this study:*

- The NDRDI incorporates national data from four different sources thus provides more robust data and strengthens the completeness of the data on drug poisoning deaths.
- Use of mortality data in addition to prescription data enabled assessment of the relationship between trends in prescribing and poisoning deaths involving specific drugs.
- Limitations of this study include the reliance on individual Coroners to implicate specific drugs in poisoning deaths, which can be challenging when multiple drugs are present on a toxicology report.
- Information on whether the drugs were prescribed for the individual is frequently not available in the sources of data, which limits the assessment of illicit use of these drugs and the impact of illicit drugs on these deaths.
- Lack of data on private prescription drugs dispensed, stratified by sex, limits analysis to those dispensed through the government assisted drug payment scheme (PCRS/GMS)

## Introduction

Drug poisonings are a leading cause of avoidable death worldwide, with rates increasing globally. National trends from the United States (U.S.) show that drug poisoning deaths have increased rapidly in recent years, with a 15% increase per year between 2013 and 2017.(1) During this period drug poisoning death rates increased in most states in the U.S., primarily due to synthetic opioids.(2) Drug poisoning deaths involving psychostimulants, especially cocaine have also increased in the U.S.(3, 4) Accidental drug poisonings are predicted to be a leading cause of premature deaths in the U.S. over the next decade, especially among women.(5) Drug poisoning deaths have also increased in Australia since 2006, with opioids being the most common drug group involved in these deaths.(6)

Similar patterns have been observed across Europe. For example, the number of drug poisoning deaths recorded in England and Scotland in 2017 was the highest ever recorded, with opioid-related deaths representing the leading cause of these deaths.(7) The European Monitoring Centre of Drugs and Drug Addiction (EMCDDA) also reported an increase in drug poisoning deaths between 2012 and 2018 in Europe, increasing from an estimated 17 deaths per million population aged 15-64 years in 2012,(8) to 22.6 deaths per million population aged 15-64 years in 2018.(9) Opioids (both licit and illicit), commonly heroin, are involved in approximately 8 out of every 10 drug poisoning deaths reported in Europe, however post-mortem toxicology analyses of poisoning deaths suggest that multiple drug toxicity is implicated in most deaths.(9)

While sex differences in drug poisoning deaths have emerged in recent years,(10) most of the available evidence fails to account for variation by sex regarding drugs involved in drug poisoning deaths.(11) Consequently as drug poisoning deaths are dominated by deaths among men, specific circumstances associated with drug poisoning deaths among women may be masked by combining trends for men and women. For example, in the U.S.,

a higher risk of drug poisoning death among young men relative to young women has been reported to be attributed to heroin and synthetic drugs.(10) In contrast, in both the U.S. and Scotland, risk of drug poisoning deaths among older women were attributed to prescription opioids, antidepressants,(12, 13) and unspecified drugs.(10) Many drug poisoning deaths involve a cocktail of CNS depressant drugs, forming a fatal combination.(14), (15) Sex-specific differences in pharmacokinetics for CNS depressant drugs such as opioids,(16) pregabalin and benzodiazepines,(17) suggest that these drugs may be impacting more on polydrug poisoning deaths among women.

Furthermore, although the absolute number of drug poisoning deaths are higher in men, epidemiological trends in Europe and the U.S. suggest the rate of drug poisoning deaths among women is increasing at a higher rate relative to men,(9, 18, 19) especially in relation to intentional drug poisoning deaths.(20)

The aim of this study is to examine sex differences in age-standardised rates of overall drug poisoning deaths, and drug poisoning deaths involving (1) any CNS depressants; (2) ≥ 2 CNS depressants; (3) and individual drug classes (e.g. prescription opioids, benzodiazepines, antidepressants, alcohol, cocaine, and heroin) in Ireland between 2004 and 2017.

This study also examines the association between dispensing rates of prescribed medications commonly implicated in drug poisoning deaths (specifically benzodiazepines and antidepressants), and drug poisoning deaths involving these agents.

## Methods

The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist for cross-sectional studies,(21) was used as a guide to structure this repeated cross-sectional study. The study was approved by the Royal College of Surgeons in Ireland Research Ethics Committee on 1st May 2018 REC 1542.

## *Patient and Public Involvement*

No patient involved.

## *Data sources*

*Drug poisoning deaths*

Design: Repeated cross-sectional study.

This study includes anonymized individual level data on all drug poisoning deaths in Ireland as recorded by the National Drug-Related Deaths Index (NDRDI) for years of death 2004 to 2017 inclusive. The NDRDI is an epidemiological database which records all poisoning deaths by drugs and/or alcohol.(22) It follows the EMCDDA standard protocol to collect data on drug-related deaths.(23) To ensure completeness, data from several sources are collected and cross-checked to avoid duplication. Coronial files are the main data source for the NDRDI. Coronial data are collected for the purpose of death investigation, thus not primarily for research, however coronial data have been recognised as a rich source of data for monitoring drug poisoning deaths.(24) Other NDRDI data sources include; the General Mortality Register via the Central Statistics Office (CSO), acute hospitals data (via the Hospital In-patient Enquiry System [HIPE]) and the national opioid agonist treatment (OAT) register, the Central Treatment List (CTL). Further details on the NDRDI methodology can be found elsewhere.(22) The methodology for collecting poisoning deaths did not change over the study period.

The NDRDI's definition of a poisoning death is a death directly due to the toxic effect of one or more drugs (including alcohol) on the body, as directed by the Coroner on the certificate of death registration and/or the record of verdict. Up to six drugs implicated in drug poisoning deaths by the Coroner are included in the NDRDI. Data on deaths which included specific drugs and drug groups, including opioids, benzodiazepines, antidepressants, Z-drugs

(zopiclone and zolpidem), pregabalin, alcohol and cocaine, were extracted from the NDRDI for this study. These are the main drugs implicated in poisoning deaths in Ireland.(15)

*Pharmacy claims data*

Aggregate level (by age, sex, year, and drug class) pharmacy claims data on prescription drugs only, including benzodiazepines and antidepressants were available from the Irish Health Service Executive (HSE) Primary Care Reimbursement Services (PCRS). This included only those with full eligibility for the General Medical Services (GMS) scheme at any time during 2004 to 2017 inclusive. Eligibility for the GMS is mainly through means-testing and age; therefore, it over-represents the more socially deprived, younger, and older aged populations in Ireland.

The HSE-PCRS pharmacy claims database funds the majority of pharmaceutical expenditure.(25) It contains details of all prescription medications dispensed to GMS eligible patients in primary care but does not include data on private prescriptions dispensed or hospital prescriptions. However, the GMS pharmacy claims database represents the single largest pharmacy claims dataset in Ireland. All claims are coded using the WHO's Anatomical Therapeutic Chemical (ATC) classification. The HSE-PCRS GMS database contains basic demographic information including age, sex, and region of residence.(25) As of 2015, almost 40% of the Irish population were covered by the GMS scheme.(25)

Data on all eligible individuals ≥16 years of age who were prescribed benzodiazepines (N05CD, N05BA or N03AE01) and/or antidepressants (N06AA, N06AB, N06AF, N06AG or N06AX), were also extracted from the HSE-PCRS GMS database and included in the study. While the GMS database records prescription opioids, it does not record methadone or buprenorphine prescriptions for the treatment of opioid dependency. Therefore, the available data on opioids was considered incomplete for the purpose of this study.

### *Study variables*

The primary outcome was drug poisoning deaths, defined as a death directly due to the toxic effect of one or more drugs (including alcohol) on the body, by sex. The secondary outcomes of interest were drug poisoning deaths involving (1) any CNS depressant drugs; (2) ≥ 2 CNS depressants drugs; and (3) individual drug classes: prescribed opioids, benzodiazepines, antidepressants, alcohol, cocaine, and heroin, by sex. If multiple drugs were implicated in an individual death then this death can be included in multiple drug categories.

For poisoning deaths involving CNS depressant drugs, any death involving at least one drug from the following drug categories; opioids (ICD 10 codes T40.2, T40.3, T40.4 and T40.6), benzodiazepines (ICD 10 code T42.4), alcohol (ICD 10 code T51), pregabalin and/or Z-drugs (ICD 10 code T42.6 with specific individual NDRDI drug codes for pregabalin, zolpidem and zopiclone identified) were combined into deaths due to 'any CNS depressant drug'. Gender, year of death and age groups (15-29, 30-44, 45-59 and ≥60 years) were also included.

### *Statistical analysis*

All analyses of trends were examined overall and separately for men and women.

*Drug poisoning deaths*

Irish general population estimates were extracted from the CSO for calculation of rates of drug poisoning deaths per 100,000 population.(26) For prescription rates the GMS eligible population for those aged 16 years and older was extracted from the PCRS annual reports.(27) The European Standard Population (ESP) was used to calculate age-standardised rates (ASR).(28)

Trends in age-standardised mortality rates (ASMR) for all drug poisoning deaths and the specific drug groups mentioned above were examined by sex while adjusting for age. Mortality rates for each year of the study period were calculated per 100,000 of the general population based on national census and projected population figures,(26) standardised to the European Standard Population (ESP).(28) Rate ratios of ASMR for men compared to women were calculated and 95% confidence intervals (CI) computed using the delta method for the variance. Joinpoint Regression Program version 4.8.0.1(29) was used to examine the overall trends in age-standardised rates from 2004 to 2017, expressed as annual percentage changes (APCs), with any changes in trends over time expressed as an average annual percentage change (AAPC). The AAPC is a summary measure which describes the average of the APCs over time. Joinpoint regression detects if there are any statistically significant trend changes in, the overall drug poisoning death rates over time, drug poisoning death rates involving any CNS depressant drugs, ≥ 2 CNS depressants drugs and for each of the drug classes described. Time periods for change in APCs were permitted to vary according to whether or not there were statistically significant change points. The APCs and the overall AAPCs are presented in the tables with results displayed by sex. A change point is a specific time point where a statistically significant trend change occurred (or a change in the APC).

*Association with prescribing patterns*

Age-standardised prescription rates (ASPR) per 1,000 of GMS eligible population for each calendar year were standardised using the relevant age categories from the ESP.

Ecological analysis of the aggregated data, using annual age-standardised rates for drug poisoning deaths and prescription data, was performed using linear regression to examine the relationship (beta regression coefficient, 95% CI) between trends in age

standardised prescription rates for benzodiazepines and antidepressants. Analyses were stratified by sex.

Statistical significance at $p < 0.05$ is assumed. Data were analysed using Joinpoint Regression Program (Version 4.8.0.1 National Cancer Institute, U.S.), and SPSS version 22 (IBM SPSS Statistics for Windows, v.22.0. Armonk, NY: IBM Corp.).

## Results

### *All drug poisoning deaths*

For the study period 2004 to 2017 there were 4,993 drug poisoning deaths recorded in Ireland. In 2004 there were 266 drug poisoning deaths (175 [66%] men; 91 [34%] women), representing an ASMR of 6.86 deaths per 100,000 (8.5 ASMR per 100,000 men and 5.0 ASMR per 100,000 women). By 2017 there were 376 drug poisoning deaths, an increase of 41.4%, (263 [70%] men; 113 [30%] women) representing an ASMR of 8.08 per 100,000 (11.5 ASMR per 100,000 men and 4.8 ASMR per 100,000 women). The rate of all drug poisoning deaths among men from 2004 to 2017 increased at an AAPC of 2.6% (95% CI, 0.2 - 5.1) (Table 1), however there was no significant change among women for the same period (Table 2). Joinpoint regression analysis identified an accelerated increase in drug poisoning deaths among men in earlier years (2004 – 2007) with no significant change in the latter years 2007 – 2017 (Table 1).

The ASMR for 2004 and 2017 by any CNS depressant drugs, ≥ 2 CNS depressant drugs, individual drug classes and individual drugs, stratified by sex are also presented in Tables 1 (men) and 2 (women).

### *CNS depressant drugs*

The rate of drug poisoning deaths involving any CNS depressant drugs increased from an ASMR of 5.61 deaths per 100,000 in 2004 to an ASMR of 6.38 per 100,000 in 2017 (Table 3). There was an AAPC increase of 2.2% (95% CI, 0.3 – 4.3) for men with an

accelerated increase noted for the period 2004 to 2008, however when drug poisoning deaths involved ≥ 2 CNS depressant drugs, men showed a higher AAPC at 5.6% (95% CI, 2.4 – 8.8) (Table 1).

For women who died of drug poisoning deaths involving any CNS depressant drugs, no significant AAPC was observed, however when ≥ 2 CNS depressant drugs were involved in the death, there was an AAPC of 4% (95% CI, 1.1 – 6.9) (Table 2).

Benzodiazepines were the main drug group implicated in all (men and women combined) drug poisoning deaths involving ≥ 2 CNS depressant drugs, implicated in 76% of these deaths.

### *Prescription Opioids*

All drug poisoning deaths involving prescription opioids, of which 61% consisted of methadone, have increased over time (Table 3) with similar AAPC for both men (3.5% [95% CI, 1.6 - 5.5]) and women (3.0% [95% CI, 0.7 - 5.3]) and no change points noted (Tables 1 & 2). Overall, 43% (n = 477) of deaths involving methadone were among people with a history of opioid dependence and registered on the national opioid agonist treatment (OAT) register, increasing from 35% (n = 14) in 2004 to 52% (n = 49) in 2017. Although fewer women are in receipt of OAT relative to men, almost two in three women (n = 185, 63%) who had methadone implicated in their death were registered on the OAT register. In contrast, just over one in three (n = 292, 36%) men, where methadone was implicated in their poisoning death, were registered on the national opioid agonist treatment (OAT) register. However it must be noted that clients can remain on the OAT register up to 30 days after dropping out of treatment, therefore it is unclear whether these deaths occurred while a person was on or off treatment.

### *Benzodiazepines*

The rate of drug poisoning deaths involving benzodiazepines increased over the observation period at an AAPC of 7.2% (95% CI, 2.9 – 11.6) among men (Table 1) and 3.3% (95% CI, 0.1 – 6.5) among women (Table 2) with no change points observed for either men or women (Table 1 & Table 2). Diazepam was the main benzodiazepine drug involved in these deaths. However, there has been a substantial increase in the number of drug poisoning deaths involving alprazolam in the latter years (supplementary file 1: Table 1) for both men and women. In 2004 alprazolam was involved in less than five deaths, rising to 63 deaths in 2017 with the majority among men (men: n = 47, 75%; women: n = 16, 25%).

For benzodiazepines, a negative relationship was observed between prescribing data and drug poisoning deaths for both men (β = -0.067, [95% CI -0.116, -0.018], p = 0.012) and women (β = -0.016, [95% CI -0.031, 0.000], p = 0.044), albeit not statistically significant for women, for the period 2004 to 2017 (Figure 1).

Insert Figure 1

### *Antidepressants*

For both men (6.1% [95% CI, 2.4 – 10.0]) and women (4.2% [95% CI, 0.2 – 8.3]) there was a significant increase in the AAPC rates for drug poisoning deaths involving antidepressants with no change points observed (Tables 1 & Table 2). Although the ASMR for women in 2017 (1.40 per 100,000) was lower than the rate in 2004 (1.71 per 100,000), the yearly rates fluctuated during the reported period with an overall upward trend. This did not result in any significant change points.

For antidepressants, a positive relationship between prescription data and drug poisoning data was observed for both men (β = 0.013, [95% CI 0.003, 0.022], p = 0.011) and women (β = 0.006, [95% CI 0.000, 0.012], p = 0.045) (Figure 2). The age standardised rate

of antidepressant items dispensed per 1000 of the GMS population increased over the study period for both men (from 153.1 per 1000 in 2004 to 218.6 per 1000 in 2017) and women (from 232.0 per 1000 in 2004 to 336.3 per 1000 in 2017).

Insert Figure 2

### *Alcohol*

The rate for women who died of drug poisoning deaths involving alcohol decreased with an AAPC decrease of 4.0% (95% CI, -5.8 – -2.1) between 2004 and 2017 (Table 2). There was no statistically significant AAPC in rates for men in the same period (Table 1). No significant change points were observed for men or women. Over half of all drug poisoning deaths involving alcohol were polydrug poisoning deaths (n =1889, 52.8%) with similar percentages for men (n = 685, 52.1%) and women (n = 312, 54.3%) (supplementary file 1: Table 1). Other CNS depressant drugs were implicated in almost a third (n = 575, 30.4%) of polydrug poisoning deaths involving alcohol. Benzodiazepines were the main other CNS depressant drug group involved in alcohol polydrug poisoning deaths, being implicated in one-in-three drug poisoning deaths involving alcohol )n = 563, 29.8%).

### *Cocaine*

Drug poisoning deaths involving cocaine fluctuated over the study period. For men, an accelerated increase was observed during the periods 2004 to 2006 and 2010 to 2017, with a significant decrease during the intervening period 2006 to 2010, giving an overall AAPC increase of 7.7% (95% CI, 2.2 – 13.6) (Table 1). Accelerated increases were also identified among women in the periods 2004 to 2008 and 2011 to 2017, however no significant AAPC was observed among women (Table 2). Although there is a higher incidence of cocaine-related drug poisoning deaths among men relative to women, the gap between men and

women is narrowing with the ASMR ratio of men to women decreasing from 11.7 in 2004 to 6.0 in 2017 (Table 3).

### *Heroin*

No trend change, for either sex, was observed for drug poisoning deaths involving heroin over the study period (Tables 1 & Table 2). While the incidence of heroin drug poisoning deaths is low among women relative to mem, the gap between men and women is reducing with the ASMR ratio of men to women decreasing from 11.7 in 2004 to 6.0 in 2017 (Table 3).

**Table 1: Age-standardised rates (ASR) (standardised to the European Standard Population) of drug poisoning deaths, per 100,000 of the general population, with APCs identified for specific change points and overall AAPCs, 2004 to 2017, among men in Ireland**

| Men | | | | | |
|---|---|---|---|---|---|
| | | †ASR per 100,000 population at change points identified | | | |
| **Drug group** | **Period** | **Start** | **End** | **APC (95% CI) %** | **AAPC (95% CI) %** |
| All drug poisoning deaths | 2004-2007 | 8.51 | 11.50 | 13.2 (1.6 to 26.1)*** | |
| | 2007-2017 | 11.50 | 11.19 | -0.3 (-1.9 to 1.2) | |
| | 2004-2017 | 8.51 | 11.19 | | 2.6 (0.2 to 5.1)*** |
| Any CNS depressant drug | 2004-2008 | 6.91 | 9.75 | 10.1 (3.3 to 17.3)*** | |
| | 2008-2017 | 9.75 | 8.57 | -1.1 (-2.7 to 0.6) | |
| | 2004-2017 | 6.91 | 8.57 | | 2.2 (0.3 to 4.3)*** |
| 2 or more CNS depressant drugs | 2004-2011 | 2.29 | 5.67 | 10.8 (5.9 to 16.0)*** | |
| | 2011-2017 | 5.67 | 4.95 | -0.2 (-5.4 to 5.3) | |
| | 2004-2017 | 2.29 | 4.95 | | 5.6 (2.4 to 8.8)*** |
| Prescription opioids | 2004-2017 | 2.76 | 3.96 | | 3.5 (1.6 to 5.5)*** |
| Benzodiazepines | 2004-2017 | 1.56 | 3.96 | | 7.2 (2.9 to 11.6)*** |
| Antidepressants | 2004-2017 | 0.70 | 1.50 | | 6.1 (2.4 to 10.0)*** |
| Alcohol | 2004-2017 | 4.12 | 3.83 | | -0.9 (-3.2 to 1.4) |
| Cocaine | 2004-2006 | 0.64 | 2.19 | 107.3 (56 to 175.6)*** | |
| | 2006-2010 | 2.19 | 0.64 | -25 (-35.1 to -13.3)*** | |
| | 2010-2017 | 0.64 | 1.58 | 9.9 (5.6 to 14.3)*** | |
| | 2004-2017 | 0.64 | 1.58 | | 7.7 (2.2 to 13.6)*** |
| Heroin | 2004-2006 | 0.61 | 2.70 | 83.4 (-33.7 to 407.7) | |
| | 2006-2017 | 2.70 | 2.64 | -1.1 (-4.5 to 2.5) | |
| | 2004-2017 | 0.61 | 2.64 | | 8.8 (-5.2 to 24.9) |

Variables significant at ***p < 0.001, ** p < 0.01, * p < 0.05.
APC = Annual percentage change. The APC was reported for time periods where a statistically significant trend change occurred
AAPC = Average annual percentage change
Change point = a specific time period where a statistically significant trend change occurred
†ASR per 100,000 population at the start and end of the change points identified and at the start and end of the study period

**Table 2: Age-standardised rates (ASR) (standardised to the European Standard Population) of drug poisoning deaths, per 100,000 of the general population, with APCs identified for specific change points and overall AAPCs, 2004 to 2017, among women in Ireland**

| Women | | | | | |
|---|---|---|---|---|---|
| | | †ASR per 100,000 population at change points identified | | | |
| **Drug group** | **Period** | **Start** | **End** | **APC (95% CI) %** | **AAPC (95% CI) %** |
| All drug poisoning deaths | 2004-2017 | 4.99 | 4.84 | | -0.5 (-2.2 to 1.2) |
| Any CNS depressant drug | 2004-2012 | 4.20 | 3.21 | -0.9 (-5.1 to 3.4) | |
| | 2012-2017 | 3.21 | 3.98 | 1.5 (-6.3 to 9.8) | |
| | 2004-2017 | 4.20 | 3.98 | | -0.0 (-3.4 to 3.5) |
| 2 or more CNS depressant drugs | 2004-2017 | 2.08 | 2.11 | | 4.0 (1.1 to 6.9)*** |
| | | | | | |
| Prescription opioids | 2004-2017 | 1.54 | 2.02 | | 3.0 (0.7 to 5.3)*** |
| Benzodiazepines | 2004-2017 | 1.70 | 1.67 | | 3.3 (0.1 to 6.5)*** |
| Antidepressants | 2004-2017 | 1.71 | 1.40 | | 4.2 (0.2 to 8.3)*** |
| Alcohol | 2004-2017 | 2.72 | 1.65 | | -4.0 (-5.8 to -2.1)*** |
| Cocaine | 2004-2008 | 0.08 | 0.45 | 61.1 (14.0 to 127.6)*** | |
| | 2008-2011 | 0.45 | 0.04 | -56.6 (-84.1 to 18.6) | |
| | 2011-2017 | 0.04 | 0.58 | 53.8 (26 to 87.8)*** | |
| | 2004-2017 | 0.08 | 0.58 | | 16.5 (-6.3 to 44.8) |
| Heroin | 2004-2017 | 0.09 | 0.47 | | 7.0 (-0.2 to 14.6) |

Variables significant at ***p < 0.001, ** p < 0.01, * p < 0.05.
APC = Annual percentage change. The APC was reported for time periods where a statistically significant trend change occurred
APC = Average annual percentage change
Change point = a specific time period where a statistically significant trend change occurred
†ASR per 100,000 population at the start and end of the change points identified and at the start and end of the study period

**Table 3: Age-standardised rates (standardised to the European Standard Population) of drug poisoning deaths, per 100,000 of the general population, 2004 to 2017, among all drug poisoning deaths in Ireland and ratio of men to women.**

| Total drug poisoning deaths | | | | |
|---|---|---|---|---|
| | Age-standardised rates per 100,000 population (95% CI) | | Ratio of men to women (95% CI) | |
| **Drug group** | **2004** | **2017** | **2004** | **2017** |
| All drug poisoning deaths | 6.86 (6.01-7.72) | 8.08 (7.25-8.91) | 1.68 (1.65-1.72) | 2.38 (2.35,2.40) |
| Any CNS depressant drug | 5.61 (4.84 -6.38) | 6.38 (5.65-7.11) | 1.62 (1.58-1.66) | 2.17 (2.14-2.19) |
| 2 or more CNS depressant drugs | 2.16 (1.69-2.63) | 3.56 (3.02-4.09) | 1.11 (1.01-1.20) | 2.35 (2.29-2.40) |
| Prescription opioids | 2.03 (1.61-2.46) | 3.01 (2.52-3.51) | 1.66 (1.56-1.76) | 1.93 (1.86-1.99) |
| Benzodiazepines | 1.59 (1.18-1.99) | 2.84 (2.36-3.32) | 0.81 (0.68-0.94) | 2.34 (2.28-2.41) |
| Antidepressants | 1.28 (0.90-1.67) | 1.47 (1.14-1.83) | 0.42 (0.22-0.62) | 1.06 (0.94-1.18) |
| Alcohol | 3.50 (2.87-4.14) | 2.79 (2.29-3.28) | 1.45 (1.38-1.52) | 2.30 (2.23-2.38) |
| Cocaine | 0.37 (0.21-0.54) | 1.02 (0.75-1.30) | 8.36 (7.26-9.44) | 2.67 (2.49-2.86) |
| Heroin | 0.60 (0.37-0.82) | 1.51 (1.17-1.85) | 11.72 (10.64-12.80) | 6.0 (5.83-6.23) |

## Discussion

### *Summary of findings*

This repeated cross-sectional study found that there was a significant increase in overall drug poisoning deaths in Ireland during the period 2004 to 2017. The ASMR for drug poisoning deaths increased among men in the early years of the study, with no significant change in the latter stage of the study period. The ASMR for overall drug poisoning deaths among women remained stable.

A similar pattern was found among men when any CNS depressant drug was implicated in poisoning deaths, with a significant increase noted only for earlier years. In contrast, no significant increase was found for deaths among women involving any CNS depressant drug.

The increasing trend for two or more CNS depressant drugs implicated in drug poisoning deaths, especially the more recent significant increase among women, is of

concern. This finding suggests that combinations of CNS depressant drugs may be impacting more on polydrug poisoning deaths in more recent years.

Our study findings differ from that reported in the U.S. where prescription opioids including fentanyl are the main drugs driving the increase in drug poisoning deaths.(2) In Ireland, while drug poisoning deaths involving prescription opioids have increased, deaths involving fentanyl remain very low.(15) Cocaine, antidepressants, and benzodiazepines; especially when combined with other CNS depressant drugs, were observed to have the highest increasing trend in drug poisoning deaths in Ireland.

Our previous research has shown a stronger association of methadone being present as part of a combination of CNS depressant drugs in drug poisoning deaths among women relative to men.(30) This current study found the majority of deaths involving prescription opioids related to methadone (both prescribed and illicit), similar to findings in the U.K.,(14) with women disproportionately affected. Although fewer women receive OAT in Ireland,(31) a higher percentage of women relative to men, who died of a drug poisoning death involving methadone, were registered for OAT at the time of their death. A growing body of evidence suggests that mortality risk during OAT is time varying.(32) As a full opioid agonist, methadone can cause hazardous respiratory depression and is associated with an elevated risk of drug poisoning during the first four weeks of treatment initiation.(32-35) The treatment timeframe for individuals included in this study is unknown. The risk of drug poisoning mortality immediately following OAT dropout, particularly the first four weeks is also high.(33-36) Given that clients' treatment status on the OAT register remains active for up to four weeks from their first day of non-attendance with their treatment provider, we cannot ascertain whether clients had dropped out of treatment. It is plausible that many clients who died of a drug poisoning death while registered on the OAT register had in fact left treatment as global evidence clearly demonstrates the protective effects of treatment

relative to leaving treatment.(37) Future work is necessary to ascertain whether the drugs involved in drug poisoning deaths vary depending on where a client is in terms of their OAT journey at the time of death.

Increased awareness among prescribers and people who use drugs of the differences between men and women in drug metabolism and drug action, and the risks associated with both prescribing and consuming multiple CNS depressant drugs is imperative. Benzodiazepines were the most common drug group in poisoning deaths involving two or more CNS depressant drugs, therefore the combination of benzodiazepines with other CNS depressant drugs warrants further investigation. Polydrug use has been recognised as an area of public health concern and has been described as "the norm" among people who use drugs.(38) Polydrug use, especially opioids with sedative drugs, including benzodiazepines, have been associated with active post-traumatic stress disorder,(39) and with serious health risks including drug poisoning deaths.(40)

This study found that for women, drug poisoning deaths involving prescription opioids, benzodiazepines and/or antidepressants increased during the study period. This result contributes to a growing body of research highlighting opioids, benzodiazepines and antidepressants as the main drugs involved in drug poisoning deaths among women.(11)

The increased availability of illicit ('street') drugs especially benzodiazepines including illicit alprazolam and diazepam and illicit prescription opioids such as methadone, certainly contribute to drug poisoning deaths. However, as the main drugs involved in drug poisoning deaths are prescription drugs which are commonly prescribed, and it is not always recorded in data sources if these drugs were prescribed to the individual or not, increased monitoring of prescribing practices in addition to enabling and enforcing use of electronic prescriptions, is required. Implementation of a national prescription monitoring system and linkage of NDRDI data to dispensed prescription data would assist in confirming whether

drug(s) involved in drug poisoning deaths were prescribed to the individual or obtained illicitly at the time of death. A national prescription monitoring system would provide important insights into the supply, availability, and appropriate prescribing of prescription drugs with potential for misuse in Ireland.

Our study showed a significant association, for both sexes, albeit marginal for women, between the rate of antidepressants dispensed and the rate of poisoning deaths involving antidepressants and while this does not indicate causality it does suggest a relationship. However, in observational studies of this sort, the possibility of residual confounding may remain a problem, therefore associations identified in this study should be viewed principally as hypothesis generating and subject to further testing and verification in future national cohort studies. Men are known to have higher rates of suicide, substance use disorder and neurodevelopment disorders relative to women.(41) Other mental health issues such as anxiety and depression are reported to be higher among women relative to men, however this may be as a result of reporting bias among men who tend to mask their symptoms more than women.(41) Taking this into consideration, the higher rates of prescribing of antidepressants among men may be an indirect indicator of more men seeking medical help for mental health issues. This increase in prescribing correlates with results from a population prevalence study which showed an increasing trend in use of antidepressants among both men and women.(42) Further research into the type of antidepressants, both dispensed and implicated in drug poisoning deaths, as well as their impact on suicide deaths by drug poisoning is necessary.

Per capita consumption of alcohol has been shown to be an important determinant of alcohol-related deaths which include drug poisoning deaths.(43) Per capita consumption of alcohol in Ireland decreased during the study period.(44) Our results are in line with this as they show a decrease in drug poisoning deaths involving alcohol over the same period, with a

significant decrease noted for women. This is a welcomed finding and may indicate a relationship between decreased consumption and decreased alcohol poisoning deaths and strengthens the need for full implementation of the Public Health (Alcohol) Bill 2018,(45) in Ireland. Of note, as alcohol is a CNS depressant, and given the high presence of other CNS depressants in polydrug poisoning deaths involving alcohol, prescribers should assess for and advise on alcohol use when prescribing CNS depressant drugs.

Following an increase in the early years of the study period, rates of drug poisoning deaths involving cocaine decreased for men and women at a time of economic recession in Ireland.(46) Our findings show that as the economy improved post-recession, there was a significant increase in cocaine-related drug poisoning deaths for both sexes, similar to that seen in other jurisdictions,(47) with the increase more substantial among women. Results from a national prevalence study during the study period also showed that while there was no significant increase in recent (last month) use of cocaine among men, there was a significant increase in recent use of cocaine among women.(42) In addition, in recent years there has been an increase in people seeking treatment related to cocaine use,(9) with an increase in the proportion of women in receipt of treatment for cocaine during the latter years of the study.(48) This trend highlights the impact of market forces on drug poisoning deaths and reflects the need to extend education and treatment related to cocaine use, especially for women.

### *Clinical and policy implications*

The increasing trend of CNS depressant drugs involved in drug poisoning deaths may indicate both increased use of these drugs to treat or cope with both addiction and other mental health issues, in addition to inappropriate, including illicit use of these drugs by individuals in the community.

Increasing awareness in both the treatment settings and in the community, of the synergistic effect of taking multiple CNS depressant drugs, including alcohol, is warranted. This should include engagement with advocacy groups who work with people who use drugs, to promote the dissemination of harm reduction information to harder to reach groups including those who are homeless. In addition, increased awareness among medical practitioners of the physiological sex differences affecting drug activity, when prescribing CNS depressant drugs is important. These differences include slower renal clearance of certain CNS depressant drugs, including pregabalin; women being more sensitive to and experience enhanced effectiveness of opioids; and benzodiazepines having a longer duration of action for women.(16, 17) Similar to that reported in other European countries,(49) Ireland does not have a national prescription drugs monitoring system. Such a system would assist with pharmacovigilance and with identifying and monitoring trends in the misuse of prescription drugs.

The significant increase in deaths involving benzodiazepines in both men and women is of concern. The decreasing rate of benzodiazepines dispensed through the PCRS/GMS system appears to correspond with changes in policy, which introduced stricter prescribing regulations.(50) However given the increase in illicit benzodiazepines in the community, as indicated by the increase in seizure data, and reports from experts in the area,(51) tighter controls on prescribing benzodiazepines may have partially resulted in an increased use of illicit benzodiazepines. These illicit benzodiazepines have higher potency and are available at low cost.(52) Due to the shorter half-life of illicit benzodiazepines, people who use these drugs tend to take repeated dosages which increases the risk of a poisoning death.

In Ireland, there were no national guidelines for benzodiazepine maintenance treatment, however in response to the COVID-19 pandemic; given the high rate of benzodiazepine misuse among homeless people on OAT, benzodiazepine maintenance

treatment was offered to homeless clients on OAT with established benzodiazepine dependency.(53) In 2019, 10% of clients in receipt of treatment for drug use in Ireland, reported benzodiazepines as their primary problem drug while 35% reported benzodiazepines as an additional problem drug.(48) While it is unknown what proportion of drug poisoning deaths since 2017 involved benzodiazepines, the United Nations Office on Drugs and Crime,(54) indicated in 2017 that polydrug use, particularly with benzodiazepines, may be linked to the increase in prescription opioid deaths. Misuse of benzodiazepines is a growing public health threat, with benzodiazepines identified as one of the most commonly misused prescription drugs.(55) Given the increasing risk of drug poisoning deaths involving benzodiazepines, continuation of and improved access to maintenance treatment along with guidelines, and detoxification for people who are known to be misusing or dependent on benzodiazepines should be considered. Research has shown that brief interventions delivered in the primary care setting are effective in both reducing and discontinuing long term benzodiazepine use.(55)

While it is disappointing to see no significant decrease in deaths involving heroin, the stabilisation of rates for drug poisoning deaths involving heroin may be due to increased access to treatment, and/or it may reflect drug markets or drug use patterns among the population. Of note, prevalence data also indicate a stabilisation in the use of heroin in the population.(42) It is known that between 2010 and 2011 there was a severe shortage of heroin in the European market,(56) the reasons for which were multifaceted. In Ireland the heroin drought was reflected in a decrease in heroin poisoning deaths in 2011, but this decrease was counterbalanced by an increase in drug poisoning deaths involving benzodiazepines and methadone.(15) The heroin drought may be an example of how despite the lack of heroin, the underlying problem of drug addiction did not dissipate. Drug markets influence changing patterns in drug use so with a decrease in availability of heroin, people

who used heroin may have had no alternative but to revert to using other drugs. This was observed in Australia, with an increase in cocaine and methamphetamine use during a period of reduced heroin availability.(57), (58)

Internationally there has been a decrease in recent years in the number of new treatment entries for OAT.(9, 48) However data from 2018 shows a significant increase in heroin seizures in the European Union.(9) This, in combination with recent evidence from Australia showing an increase in deaths involving heroin,(59) indicates that heroin remains a main contributor to drug-related harm including drug poisoning deaths worldwide.

Although beyond the scope of this study, it would be of interest to assess the impact of the codeine dispensing guidelines for non-prescription products containing codeine, introduced in Ireland in 2010,(60) on drug poisoning deaths involving opioids.

In an effort to prevent drug poisoning deaths among both men and women, a combination of pharmacological, psychosocial and harm reduction interventions, with increasing access to sex-specific and age appropriate treatment and wider availability of naloxone, should be implemented.(61, 62) Promoting more open communication between prescribers and clients should enhance provision of appropriate treatment and help clients make informed decisions about their drug use. Innovative models of virtual healthcare delivery, such as those adapted during the COVID-19 pandemic, could also help minimise barriers to accessing services. Consideration should be given to incorporating this model of care, in addition to face to face consultations in future delivery of care.(63) In addition services tailored to the particular needs of women are required, such as increasing the number of residential treatment beds with childcare facilities.

Advocates for people who use drugs should be consulted on and contribute to policy decisions around reducing harms associated with drug use. Policies to reduce drug poisoning deaths should move from a criminal justice focus to a more public health focus.(64, 65)

Harm reduction initiatives along with treatment interventions, which include pharmaceutical combined with psychosocial assistance, need to focus on the range of problematic drugs. Furthermore, reducing stigma associated with drug use and drug poisoning deaths, aligned with actions to target economic deprivation, are required.

Future research in the area of drug poisoning deaths should include stratification by sex. Sex-specific evidence is required to support appropriate policy actions to reduce drug poisoning deaths.

## Strengths and limitations

The main strength of this study is the use of national data validated from a number of sources, ensuring accuracy and completeness of data available to examine trends in drug poisoning deaths by sex. Access to prescription data for prescribed benzodiazepines and antidepressants enabled assessment of the relationship between trends in prescribing for and drug poisoning death rates involving these drugs.

Due to the nature of the death investigation and data collection processes, more recent data on drug poisoning deaths was not available. Future work will need to assess whether there have been any trend changes since 2017. However given that the observation period of 2004 to 2017 was used in this study this strengthens the completeness of the data.

Limitations of this study include the reliance on individual Coroners to implicate drugs in poisoning deaths, which can be challenging when multiple drugs are present on a toxicology report. Information on whether the drugs were prescribed to the individual is frequently not available in coronial files which limits the assessment of illicit use of these drugs and the impact of illicit drugs on these deaths.

Lack of data on private prescription drugs dispensed, limits analysis to those dispensed through the PCRS/GMS scheme, which covers approximately 40% of the general population. The PCRS/GMS scheme over-represents the more socially deprived and older

aged populations, and therefore, does not represent the total population use of these drugs. Also, the lack of data on consumption of other drugs, including prescription opioids, alcohol, cocaine, and heroin, stratified by sex, limited the analysis on these drugs.

Clients registered on the national opioid agonist treatment register can remain registered up to 30 days after leaving treatment. Therefore, data on clients in receipt of prescription opioids at the time of their death is incomplete. For this reason we were not able to assess the relationship between dispensing of prescription opioids and deaths involving prescription opioids.

## Conclusion

There is a need for an efficient healthcare response to polydrug use, which should include pragmatic harm reduction information around potentially lethal combinations of drugs, including alcohol, and how to reduce consumption of multiple drugs, especially CNS depressant drugs. Increased awareness of physiological sex differences affecting drug activity is required among both prescribers and people who use drugs. In addition to endorsement of a nationwide ePrescription system, an active national prescription monitoring system would assist in increased pharmacovigilance.

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## Declaration of Competing interest

No conflict declared.

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## Author contributions

Ena Lynn, Professor Kathleen Bennett, and Dr Gráinne Cousins designed the study. Ena Lynn was responsible for the writing of the manuscript and undertook the statistical analysis with guidance from Professor Kathleen Bennett and Dr Grainne Cousins. All authors provided critical input to drafts of the paper. All authors contributed to the interpretation of the data and approved the final manuscript.

## References


1. Shiels M S, Tatalovich Z, Chen Y, et al. Trends in Mortality From Drug poisonings, Suicide, and Alcohol-Induced Deaths in the United States From 2000 to 2017. *JAMA Netw Open,* 2020;**3**:e2016217. doi.org/10.1001/jamanetworkopen.2020.16217
2. Scholl L, Seth P, Kariisa M, et al. Drug and Opioid-Involved Overdose Deaths - United States, 2013-2017. *MMWR: Morb Mortal Wkly Rep,* 2019;67:1419-1427. doi.org/10.15585/mmwr.mm675152e1
3. Seth P, Scholl L, Rudd R. A, et al. Overdose Deaths Involving Opioids, Cocaine, and Psychostimulants - United States, 2015-2016. *Morb Mortal Wkly Rep,* 2018;**67**:349-358. doi.org/10.15585/mmwr.mm6712a1
4. McCall Jones C, Baldwi, G. T & Compton W M. Recent Increases in Cocaine-Related Overdose Deaths and the Role of Opioids. *American Journal of Public Health,* 2017;107:430-432. doi.org/10.2105/AJPH.2016.303627
5. Best A F, Haozous E A, Berrington de Gonzalez A, et al. Premature mortality projections in the USA through 2030: a modelling study. *Lancet Public Health,* 2018;3:e374-e384. doi.org/10.1016/S2468-2667(18)30114-2
6. Man N, Chrzanowska A, Dobbins T, et al. Trends in drug-induced deaths in Australia, 1997-2018. Drug Trends Bulletin Series. Sydney: National Drug and Alcohol Research Centre. 2019. https://ndarc.med.unsw.edu.au/resource/trends-drug-induced-deaths-australia-1997-2018 (accessed Sept 2020)
7. Kimber J, Hickman M, Strang J, et al. Rising opioid-related deaths in England and Scotland must be recognised as a public health crisis. *Lancet Psychiatry,* 2019;6:639-640. doi.org/10.1016/S2215-0366(19)30209-3

8. EMCDDA. European Drug Report 2014: Trends and Developments. 2014 https://www.emcdda.europa.eu/publications/edr/trends-developments/2014_en (assessed Oct 2020)

9. EMCDDA. European Drug Report 2020: Trends and Developments. 2020. https://www.emcdda.europa.eu/publications/edr/trends-developments/2020_en (assessed 25 Sept 2020)

10. Jalal H, Buchanich J M, Roberts M S et al. Changing dynamics of the drug overdose epidemic in the United States from 1979 through 2016. *Science,* 2018;361:6408. doi.org/10.1126/science.aau1184

11. Lynn E, Doyle A, Keane M, et al. Drug poisoning deaths among women: a scoping review. *J Stud Alcohol Drugs,* 2020;81:543-555. doi.org/10.15288/jsad.2020.81.543

12. Tweed E, Miller R, Mathesone C. Why are drug-related deaths among women increasing in Scotland? A scoping of possible explanations. Edinburgh: Scottish Government. 2018. http://www.gov.scot/publications/drug-related-deaths-women-increasing-scotland-9781787810129/(assessed Sept 2020)

13. Centers for Disease Control and Prevention. Prescription Painkiller Overdoses: A Growing Epidemic, Especially Among Women. 2013. https://www.cdc.gov/vitalsigns/prescriptionpainkilleroverdoses/index.html (assessed 7 March 2020)

14. Corkery JM, Schifano F, Ghodse AH, Oyefeso A. The effects of methadone and its role in fatalities. Hum Psychopharmacol. 2004; 19(8): 565-76. doi.org/10.1002/hup.630

15. Health Research Board. National Drug-Related Deaths Index 2008 to 2017 data. Health Research Board; 2019. https://www.drugsandalcohol.ie/31275 (assessed Oct 2020)

16. Algren D A, Monteilh C P, Punja M, et al. Fentanyl-associated fatalities among illicit drug users in Wayne County, Michigan (July 2005-May 2006). *Journal of Medical Toxicology,* 2013;9:106-115. doi.org/10.1007/s13181-012-0285-4

17. Whitley H, Lindsey W. Sex-based differences in drug activity. *Am Fam Physician,* 2009;80:1254-1258. doi.org/10.1016/S0140-6736(19)31812-4

18. VanHouten J P, Rudd R A, Ballesteros M F, et al. Drug Overdose Deaths Among Women Aged 30-64 Years - United States, 1999-2017. *MMWR: Morb Mortal Wkly Rep,* 2019;68:1-5. doi.org/10.15585/mmwr.mm6801a1

19. Osborn E. Deaths related to drug poisoning in England and Wales: 2017 registrations. Statistical bulletin. Office for National Statistics; 2018. https://www.ons.gov.uk/releases/deathsrelatedtodrugpoisoninginenglandandwales2017registrations (assessed Oct 2020).

20. Tyrrell E G, Orton E, Sayal K, et al. Differing patterns in intentional and unintentional poisonings among young people in England, 1998–2014: a population-based cohort study. *J Public Health (Oxf),* 2017;39:e1-e9. doi.org/10.1093/pubmed/fdw075

21. STROBE Statement. STROBE Statement. https://www.strobe-statement.org/fileadmin/Strobe/uploads/checklists/STROBE_checklist_v4_combined.pdf (assessed 30 May 2019)

22. Lynn E, Lyons S, Walsh S, et al. Trends in deaths among drug users in Ireland from traumatic and medical causes, 1998 to 2005. 2019 Dublin: Health Research Board. https://www.drugsandalcohol.ie/12775/ (assessed Sept 2020)

23. EMCDDA. Drug-Related Deaths (DRD) Standard Protocol, version 3.2. Lisbon: EMCDDA. 2010 https://www.emcdda.europa.eu/html.cfm/index107404EN.html_en (assessed Sept 2020)

24. Roxburgh A, Pilgrim J L, Hall W D, et al. Accurate identification of opioid overdose deaths using coronial data. *Forensic Sci Int,* 2018;287:40-46. doi.org/10.1016/j.forsciint.2018.03.032

25. Sinnott S J, Bennett K, Cahir C. Pharmacoepidemiology resources in Ireland-an introduction to pharmacy claims data. *Eur J Clin Pharmacol,* 2017;73:1449-1455. doi.org/10.1007/s00228-017-2310-7

26. Central Statistics Office. StatBank Annual Population Estimates. 2020. https://statbank.cso.ie/px/pxeirestat/Statire/SelectVarVal/Define.asp?maintable=PEA01&PLanguage=0 (assessed 15 Feb 2020)

27. Health Service Executive. Primary Care Reimbursement Service: Statistical Analysis of Claims and Payments 2008 to 2017. 2017. https://www.sspcrs.ie/portal/annual-reporting/report/annual (assessed 12 Sept 2020)

28. Eurostat. Revision of the European Standard Population – Report of Eurostat's Task Force. Luxembourg: European Commission. 2013. doi.org/10.2785/11470 (assessed Feb 2020)

29. National Cancer Institute. Joinpoint trend analysis softward. 2020 https://surveillance.cancer.gov/joinpoint/ (assessed 4 Aug 2020)

30. Lynn E, Cousins G, Lyons S, et al. A repeated cross-sectional study of factors associated with pregabalin-positive poisoning deaths in Ireland. *Drug Alcohol Depend,* 2020;206:107741. doi.org/10.1016/j.drugalcdep.2019.107741

31. Cousins G, Boland F, Barry J, et al. J-shaped relationship between supervised methadone consumption and retention in methadone maintenance treatment (MMT) in primary care: National cohort study. *Drug Alcohol Depend,* 2017;173: 126-131. doi.org/10.1016/j.drugalcdep.2016.12.009

32. Sordo L, Barrio G, Bravo M J, et al. Mortality risk during and after opioid substitution treatment: systematic review and meta-analysis of cohort studies. *Br Med J*, 2017;357: j1550. doi.org/10.1136/bmj.j1550

33. Cousins G, Teljeur C, Motterlini N, et al. Risk of drug-related mortality during periods of transition in methadone maintenance treatment: A cohort study. *J Subst Abuse Treat,* 2011;41:252-260. doi.org/10.1016/j.jsat.2011.05.001

34. Durand L, O'Driscoll D, Boland F, et al. Do interruptions to the continuity of methadone maintenance treatment in specialist addiction settings increase the risk of drug-related poisoning deaths? A retrospective cohort study. *Addiction*. 2020;115:1867-1877. doi.org/10.1111/add.15004

35. Evans E, Li L, Min J, et al. Mortality among individuals accessing pharmacological treatment for opioid dependence in California, 2006-10. *Addiction,* 2015;**110**:996-1005. doi.org/10.1111/add.12863

36. Kimber J, Larney S, Hickman M, et al. Mortality risk of opioid substitution therapy with methadone versus buprenorphine: a retrospective cohort study. *Lancet Psychiatry*, 2015;2:901-908. doi.org/10.1016/s2215-0366(15)00366-1

37. Santo T, Jr, Clark B, Hickman M, Grebely J, Campbell G, Sordo L, et al. Association of Opioid Agonist Treatment With All-Cause Mortality and Specific Causes of Death Among People With Opioid Dependence: A Systematic Review and Meta-analysis. JAMA Psychiatry. 2021. doi.org/10.1001/jamapsychiatry.2021.0976

38. Jarlenski M, Barry C L, Gollust S, et al. Polysubstance Use Among US Women of Reproductive Age Who Use Opioids for Nonmedical Reasons. *Am J Public Health,* 2017;107:1308-1310. doi.org/10.2105/AJPH.2017.303825

39. Hassan A, Le Foll B. Polydrug use disorders in individuals with opioid use disorder. *Drug Alcohol Depend,* 2019;198:28-33. doi.org/10.1016/j.drugalcdep.2019.01.031

40. Calcaterra S, Glanz J, Binswanger I. National trends in pharmaceutical opioid related overdose deaths compared to other substance related overdose deaths: 1999–2009. *Drug Alcohol Depend,* 2013;131:263-270. doi.org/10.1016/j.drugalcdep.2012.11.018

41. Affleck W, Carmichael V, Whitley R. Men's Mental Health: Social Determinants and Implications for Services. *Can J Psychiatry.* 2018;63:581-589. doi.org/10.1177/0706743718762388

42. National Advisory Committee on Drugs and Alcohol, Northern Ireland. Department of Health. Prevalence of drug use and gambling in Ireland & drug use in Northern Ireland. Bulletin 1. Dublin: National Advisory Committee on Drugs and Alcohol. 2016. https://www.drugsandalcohol.ie/26364/(assessed Oct 2020)

43. Norström T, Mäkelä,P. The connection between per capita alcohol consumption and alcohol-specific mortality accounting for unrecorded alcohol consumption: The case of Finland 1975–2015. *Drug Alcohol Rev*, 2019;38:731-736. doi.org/10.1111/dar.12983

44. Office of Revenue Commissioners. Excise Receipts by Commodity. 2020. https://www.revenue.ie/en/corporate/information-about-revenue/statistics/excise/receipts-volume-and-price/excise-receipts-commodity.aspx (assessed 4 July 2020)

45. Government of Ireland. Public Health (Alcohol) Act 2018. 2018. http://www.irishstatutebook.ie/eli/2018/act/24/enacted/en/html (assessed 14 Sept 2020)

46. Eurostat. General government deficit/surplus: % of GDP and million EUR. 2020.https://ec.europa.eu/eurostat/databrowser/view/tec00127/default/table?lang=en (assessed 23 Sept 2020)

47. Hedegaard H, Spencer M R, Garnett M F. Increase in drug overdose deaths involving cocaine: United States, 2009–2018. NCHS Data Brief No.384. Centre for Disease Control and Prevention. 2020. https://www.cdc.gov/nchs/data/databriefs/db384-H.pdf (assessed Oct 2020)

48. O'Neill D, Carew A, Lyons S. Drug Treatment in Ireland 2013 to 2019. Dublin: Health Research Board. 2020. https://www.drugsandalcohol.ie/32094 (assessed 19 Sept 2020)

49. Novak SP, Håkansson A, Martinez-Raga J, Reimer J, Krotki K, Varughese S. Nonmedical use of prescription drugs in the European Union. BMC Psychiatry. 2016;16(1):274. doi.org/10.1186/s12888-016-0909-3

50. Benzodiazepine Committee. Benzodiazepines: good practice guidelines for clinicians. Dublin: Department of Health and Children. 2002. https://www.drugsandalcohol.ie/5349/(assessed 27 Sept 2020)

51. Duffin T, Keane M, Millar S R. Street tablet use in Ireland. A Trendspotter study on use, markets, and harms. Dublin: Ana Liffey Drug Project. 2020. https://www.drugsandalcohol.ie/31872/(assessed Oct 2020)

52. Ryan V. 'Fake' benzos potency fears rise. *Irish Medical Times*. Dublin. 2020. https://www.imt.ie/news/fake-benzos-potency-fears-rise-31-08-2020/(assessed 31 Aug 2020)

53. O'Carroll A, Duffin T, Collins J. Harm reduction in the time of COVID-19: Case study of homelessness and drug use in Dublin, Ireland. *Int J Drug Policy,* 2021;87:102966. doi.org/10.1016/j.drugpo.2020.102966

54. UNODC. Global Smart Update Volume 18: Non-medical use of benzodiazepines: a growing threat to public health? ; 2017.

https://www.unodc.org/documents/scientific/Global_SMART_Update_2017_Vol_18.pdf (assessed 13 June 2021)

55. Lynch T, Ryan C, Hughes C M, et al. Brief interventions targeting long-term benzodiazepine and Z-drug use in primary care: a systematic review and meta-analysis. *Addiction,* 2020;115:1618-1639. doi.org/10.1111/add.14981

56. EMCDDA. Trendspotter Summary Report Recent Shocks in the European Heroin Market: Explanations and Ramifications In. Lisbon: EMCDDA. 2011. https://www.emcdda.europa.eu/scientific-studies/2011/trendspotters-report_en (assessed Oct 2020)

57. Roxburgh A, Degenhardt L, Breen C. Changes in patterns of drug use among injecting drug users following changes in the availability of heroin in New South Wales, Australia. Drug Alcohol Rev. 2004;23(3):287-94. doi:10.1080/09595230412331289446

58. Degenhardt L, Conroy E, Gilmour S, Collins L. THE EFFECT OF A REDUCTION IN HEROIN SUPPLY IN AUSTRALIA UPON DRUG DISTRIBUTION AND ACQUISITIVE CRIME. The British Journal of Criminology. 2005;45(1):2-24. doi:10.1093/bjc/azh096

59. Australian Institute of Health and Welfare. Alcohol, tobacco & other drugs in Australia. 2020. https://www.aihw.gov.au/reports/phe/221/alcohol-tobacco-other-drugs-australia/contents/drug-types/illicit-opioids-heroin (assessed 3 Sept 2020)

60. The Pharmaceutical Society of Ireland. Non-prescription medicinal products containing codeine: Guidance for pharmacists on safe supply to patients. Dublin: The Pharmaceutical Society of Ireland. 2010. www.drugsandalcohol.ie/13191 (assessed 6 Oct 2020)

61. Fairbairn N, Coffin P O, Walley A Y. Naloxone for heroin, prescription opioid, and illicitly made fentanyl overdoses: Challenges and innovations responding to a dynamic epidemic. *Int J Drug Policy,* 2017;46:172-179. doi.org/10.1016/j.drugpo.2017.06.005

62. Degenhardt L, Grebely J, Stone J, et al. Global patterns of opioid use and dependence: harms to populations, interventions, and future action. *Lancet,* 2019;394:1560-1579. doi.org/10.1016/S0140-6736(19)32229-9

63. Crowley D, Delargy I. A national model of remote care for assessing and providing opioid agonist treatment during the COVID-19 pandemic: a report. *Harm Reduct J,* 2020;17:49. doi.org/10.1186/s12954-020-00394-z

64. EMCDDA. Health and social responses to drug problems: a European guide. 2017. https://www.emcdda.europa.eu/publications/manuals/health-and-social-responses-to-drug-problems-a-european-guide_en (assessed 20 Sept 2020)

65. UNODC. Treatment and Care of people with Drug Use Disorders in Contact with the Criminal Justice System: Alternatives to Conviction or Punishment. 2016.https://www.unodc.org/unodc/en/drug-prevention-and-treatment/treatment-and-care-of-people-with-drug-use-disorders-in-contact-with-the-criminal-justice-system_-alternatives-to-conviction-or-punishment.html (assessed Oct 2020)

Figure 1. Benzodiazepines: Age-standardised rates per 100,000 of drug poisoning deaths involving benzodiazepines and age-standardised rates per 1,000 of individuals in receipt of prescribed benzodiazepines through the GMR/PCRS; 2004 to 2017.

Figure 2. Antidepressants: Age-standardised rates per 100,000 of drug poisoning deaths involving antidepressants and age-standardised rates per 1,000 of individuals in receipt of prescribed antidepressants through the GMR/PCRS; 2004 to 2017.

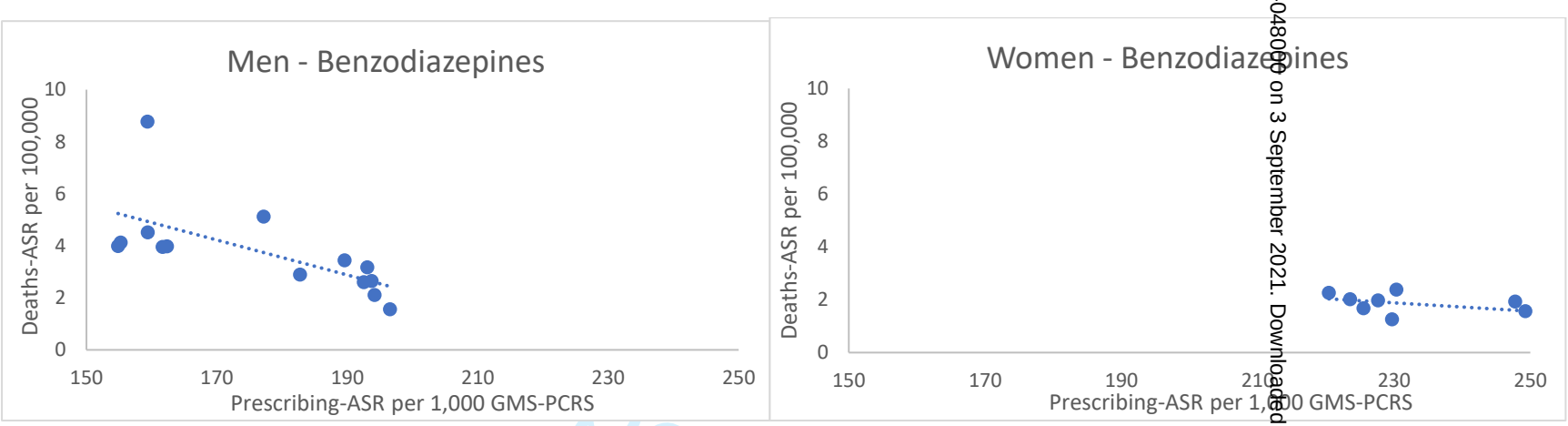


Figure 1. Benzodiazepines: Age-standardised rates per 100,000 of drug poisoning deaths involving benzodiazepines and age-standardised rates per 1,000 of individuals in receipt of prescribed benzodiazepines through the GMR/PCRS; 2004 to 2017.

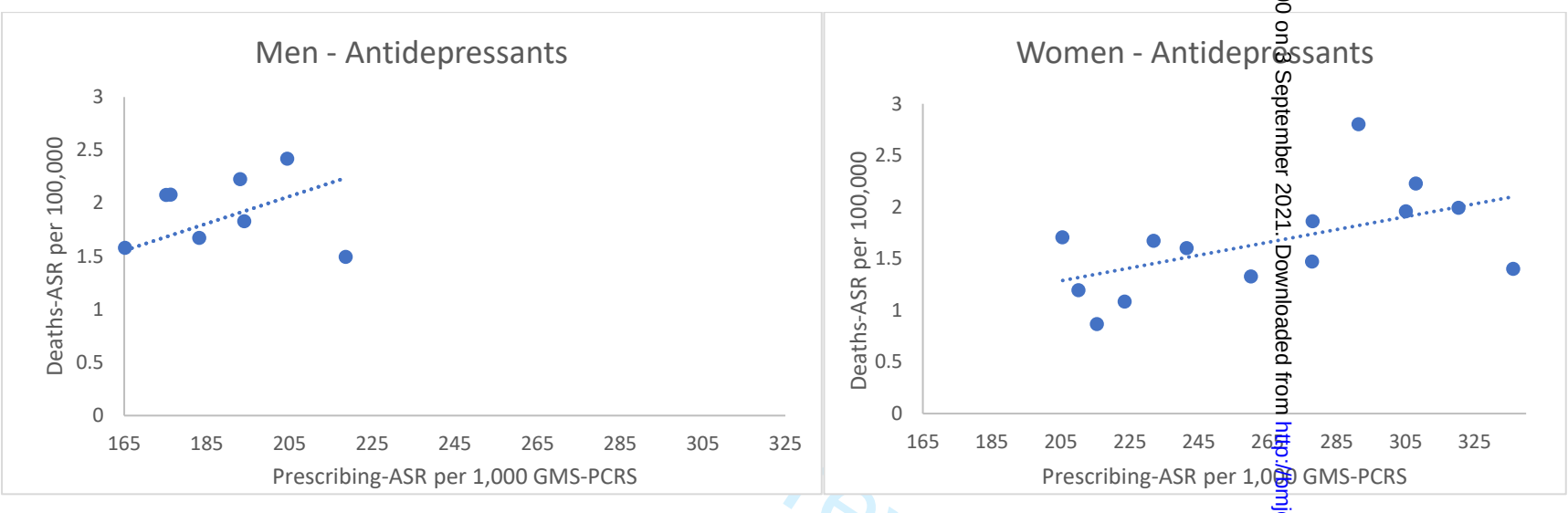


Figure 2. Antidepressants: Age-standardised rates per 100,000 of drug poisoning deaths involving antidepressants and age-standardised rates per 1,000 of individuals in receipt of prescribed antidepressants through the GMR/PCRS; 2004 to 2017.

**Supplementary Table 4ʏ: Number of individual drug poisoning deaths, with breakdown of age group and drugs involved, by sex, NDRDI 2004 to 2017**

| | 2004 - 2005 n (%) | | | | 2006 - 2007 n (%) | | | | 2008 - 2009 n (%) | | | | 2010 - 2011 n (%) | | | | 2012 - 2013 n (%) | | | | 2014 - 2015 n (%) | | | | 2016 - 2017 n (%) | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Men | Women | Total | % of total | Men | Women | Total | % of total | Men | Women | Total | % of total | Men | Women | Total | % of total | Men | Women | Total | % of total | Men | Women | Total | % of total | Men | Women | Total | % of total |
| All drug poisoning deaths | 374 (66.1) | 192 (33.9) | 566 | | 497 (69.8) | 215 (30.2) | 712 | | 527 (69.5) | 231 (30.5) | 758 | | 525 (73.3) | 191 (26.7) | 716 | | 537 (70.9) | 220 (29.1) | 757 | | 510 (68.9) | 230 (31.1) | 740 | | 512 (68.8) | 232 (31.2) | 744 | |
| **Age Groups** | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| *13 to 24 years of age* | 77 (77.8) | 22 (22.2) | 99 | 17.5 | 93 (81.6) | 21 (18.4) | 114 | 16.0 | 68 (85.0) | 12 (15.0) | 80 | 10.6 | 68 (82.9) | 14 (17.1) | 82 | 11.5 | 57 (78.1) | 16 (21.9) | 73 | 9.6 | 42 (75.0) | 14 (25.0) | 56 | 7.6 | 35 (87.5) | 5 (12.5) | 40 | 5.4 |
| *25 to 34 years of age* | 104 (78.8) | 28 (21.2) | 132 | 23.3 | 163 (78.0) | 46 (22.0) | 209 | 29.4 | 169 (74.4) | 58 (25.6) | 227 | 29.9 | 145 (81.5) | 33 (18.5) | 178 | 24.9 | 173 (82.4) | 37 (17.6) | 210 | 27.7 | 135 (73.8) | 48 (26.2) | 183 | 24.7 | 104 (76.5) | 32 (23.5) | 136 | 18.3 |
| *35 to 44 years of age* | 71 (68.3) | 33 (31.7) | 104 | 18.4 | 116 (68.6) | 53 (31.4) | 169 | 23.7 | 136 (78.6) | 37 (21.4) | 173 | 22.8 | 148 (78.3) | 41 (21.7) | 189 | 26.4 | 129 (73.7) | 46 (26.3) | 175 | 23.1 | 171 (76.0) | 54 (24.0) | 225 | 30.4 | 164 (68.3) | 76 (31.7) | 240 | 32.3 |
| *45 to 54 years of age* | 75 (55.6) | 60 (44.4) | 135 | 23.9 | 75 (62.5) | 45 (37.5) | 120 | 16.9 | 83 (60.6) | 54 (39.4) | 137 | 18.1 | 93 (65.5) | 49 (34.5) | 142 | 19.8 | 98 (66.2) | 50 (33.8) | 148 | 19.6 | 86 (66.7) | 43 (33.3) | 129 | 17.4 | 123 (73.7) | 44 (26.3) | 167 | 22.4 |
| *55 or more years of age* | 47 (49.0) | 49 (51.0) | 96 | 17.0 | 50 (50.0) | 50 (50.0) | 100 | 14.0 | 71 (50.4) | 70 (49.6) | 141 | 18.6 | 71 (56.8) | 54 (43.2) | 125 | 17.5 | 80 (53.0) | 71 (47.0) | 151 | 19.9 | 76 (51.7) | 71 (48.3) | 147 | 19.9 | 86 (53.4) | 75 (46.6) | 161 | 21.6 |
| | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| **Polydrugs (≥2 drugs) involved in the death** | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| *Yes* | 154 (60.9) | 99 (39.1) | 253 | 44.7 | 219 (67.8) | 104 (32.2) | 323 | 44.7 | 271 (70.0) | 116 (30.0) | 387 | 44.7 | 287 (72.3) | 110 (27.7) | 397 | 44.7 | 300 (68.6) | 137 (31.4) | 437 | 44.7 | 320 (67.7) | 153 (32.3) | 473 | 44.7 | 294 (65.8) | 153 (34.2) | 447 | 44.7 |
| *No* | 220 (70.3) | 93 (29.7) | 313 | 55.3 | 278 (71.5) | 111 (28.5) | 389 | 55.3 | 256 (69.0) | 115 (31.0) | 371 | 55.3 | 238 (74.6) | 81 (25.4) | 319 | 55.3 | 237 (74.1) | 83 (25.9) | 320 | 55.3 | 190 (71.2) | 77 (28.8) | 267 | 55.3 | 218 (73.4) | 79 (26.6) | 297 | 55.3 |
| | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| **CNS depressant drugs involved in the death** | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| *Yes* | 291 (66.1) | 149 (33.9) | 440 | 77.7 | 395 (60.4) | 169 (25.8) | 564 | 79.2 | 442 (70.8) | 182 (29.2) | 624 | 82.3 | 460 (74.1) | 161 (25.9) | 621 | 86.7 | 449 (72.3) | 172 (27.7) | 621 | 82.0 | 430 (69.4) | 190 (30.6) | 620 | 83.8 | 417 (68.2) | 194 (31.8) | 611 | 82.1 |
| *No* | 83 (65.9) | 43 (34.1) | 126 | 22.3 | 102 (68.9) | 46 (31.1) | 148 | 20.8 | 85 (63.4) | 49 (36.6) | 134 | 17.7 | 65 (68.4) | 30 (31.6) | 95 | 13.3 | 88 (64.7) | 48 (35.3) | 136 | 18.0 | 80 (66.7) | 40 (33.3) | 120 | 16.2 | 95 (71.4) | 38 (28.6) | 133 | 17.9 |
| *Breakdown of CNS depressants drugs* | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| *Opioids (prescription (63%), heroin (37%))* | 194 (71.6) | 77 (28.4) | 271 | 61.6 | 272 (76.4) | 84 (23.6) | 356 | 63.1 | 334 (76.3) | 104 (23.7) | 438 | 70.2 | 328 (78.3) | 91 (21.7) | 419 | 67.5 | 340 (76.6) | 104 (23.4) | 444 | 71.5 | 346 (71.8) | 136 (28.2) | 482 | 77.7 | 321 (70.9) | 132 (29.1) | 453 | 74.1 |
| *Alcohol* | 150 (62.2) | 91 (37.8) | 241 | 54.8 | 192 (67.1) | 94 (32.9) | 286 | 50.7 | 203 (67.7) | 97 (32.3) | 300 | 48.1 | 216 (73.7) | 77 (26.3) | 293 | 47.2 | 202 (74.3) | 70 (25.7) | 272 | 43.8 | 165 (70.5) | 69 (29.5) | 234 | 37.7 | 186 (70.7) | 77 (29.3) | 263 | 43.0 |
| *Benzodiazepines* | 78 (60.5) | 51 (39.5) | 129 | 29.3 | 120 (63.8) | 68 (36.2) | 188 | 33.3 | 160 (73.7) | 57 (26.3) | 217 | 34.8 | 198 (72.5) | 75 (27.5) | 273 | 44.0 | 209 (71.8) | 82 (28.2) | 291 | 46.9 | 212 (67.9) | 100 (32.1) | 312 | 50.3 | 197 (68.4) | 91 (31.6) | 288 | 47.1 |
| Z-Drugs | 8 (50.0) | 8 (50.0) | 16 | 3.6 | 11 (55.0) | 9 (45.0) | 20 | 3.5 | 18 (64.3) | 10 (35.7) | 28 | 4.5 | 34 (61.8) | 21 (38.2) | 55 | 8.9 | 59 (67.8) | 28 (32.2) | 87 | 14.0 | 88 (56.8) | 67 (43.2) | 155 | 25.0 | 72 (58.5) | 51 (41.5) | 123 | 20.1 |
| *Pregabalin* | 0 | 0 | 0 | | 0 | 0 | 0 | | 0 | ~ | ~ | ~ | ~ | ~ | ~ | ~ | 7 (46.7) | 8 (53.3) | 15 | 2.4 | 34 (44.2) | 43 (55.8) | 77 | 12.4 | 63 (57.8) | 46 (42.2) | 109 | 17.8 |
| **2 or more CNS depressant drugs involved** | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| *Yes* | 117 (62.9) | 69 (37.1) | 186 | 32.9 | 163 (68.5) | 75 (31.5) | 238 | 33.4 | 208 (74.6) | 71 (25.4) | 279 | 36.8 | 235 (74.1) | 82 (25.9) | 317 | 44.3 | 251 (72.8) | 94 (27.2) | 345 | 45.6 | 269 (67.8) | 128 (32.2) | 397 | 53.6 | 248 (67.0) | 122 (33.0) | 370 | 49.7 |
| *No* | 257 (67.6) | 123 (32.4) | 380 | 67.1 | 334 (70.5) | 140 (29.5) | 474 | 66.6 | 319 (66.6) | 160 (33.4) | 479 | 63.2 | 290 (72.7) | 109 (27.3) | 399 | 55.7 | 286 (69.4) | 126 (30.6) | 412 | 54.4 | 241 (70.3) | 102 (29.7) | 343 | 46.4 | 264 (70.6) | 110 (29.4) | 374 | 50.3 |
| *Breakdown of ≥2 CNS depressants drugs* | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| *Opioids (prescription (63%), heroin (37%))* | 114 (71.3) | 46 (28.8) | 160 | 86.0 | 153 (75.4) | 50 (24.6) | 203 | 85.3 | 212 (77.1) | 63 (22.9) | 275 | 98.6 | 235 (79.7) | 60 (20.3) | 295 | 93.1 | 267 (77.8) | 76 (22.2) | 343 | 99.4 | 281 (71.1) | 114 (28.9) | 395 | 99.5 | 258 (71.1) | 105 (28.9) | 363 | 98.1 |
| *Benzodiazepines* | 73 (59.8) | 49 (40.2) | 122 | 65.6 | 113 (65.3) | 60 (34.7) | 173 | 72.7 | 157 (75.8) | 50 (24.2) | 207 | 74.2 | 191 (73.7) | 68 (26.3) | 259 | 81.7 | 200 (72.5) | 76 (27.5) | 276 | 80.0 | 205 (68.3) | 95 (31.7) | 300 | 75.6 | 193 (68.9) | 87 (31.1) | 280 | 75.7 |
| *Alcohol* | 62 (57.4) | 46 (42.6) | 108 | 58.1 | 86 (66.7) | 43 (33.3) | 129 | 54.2 | 97 (72.9) | 36 (27.1) | 133 | 47.7 | 98 (72.6) | 37 (27.4) | 135 | 42.6 | 86 (75.4) | 28 (24.6) | 114 | 33.0 | 86 (68.8) | 39 (31.2) | 125 | 31.5 | 88 (68.8) | 40 (31.3) | 128 | 34.6 |
| Z-Drugs | 7 (53.8) | 6 (46.2) | 13 | 7.0 | 11 (57.9) | 8 (42.1) | 19 | 8.0 | 15 (65.2) | 8 (34.8) | 23 | 8.2 | 27 (57.4) | 20 (42.6) | 47 | 14.8 | 55 (67.9) | 26 (32.1) | 81 | 23.5 | 81 (56.3) | 63 (43.8) | 144 | 36.3 | 66 (57.4) | 49 (42.6) | 115 | 31.1 |
| *Pregabalin* | 0 | 0 | 0 | | 0 | 0 | 0 | | 0 | ~ | ~ | ~ | ~ | ~ | ~ | ~ | 6 (42.9) | 8 (57.1) | 14 | 4.1 | 30 (41.7) | 42 (58.3) | 72 | 18.1 | 60 (57.7) | 44 (42.3) | 104 | 28.1 |

| | | | | | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Rx Opioids** | 125 (64.1) | 70 (35.9) | 195 | 34.5 | 137 (66.2) | 70 (33.8) | 207 | 29.1 | 156 (67.0) | 77 (33.0) | 233 | 30.7 | 208 (73.5) | 75 (26.5) | 283 | 39.5 | 201 (68.8) | 91 (31.2) | 292 | 38.6 | 192 (63.8) | 109 (36.2) | 301 | 40.7 | 192 (63.6) | 110 (36.4) | 302 | 40.6 |
| *Of which the main drugs involved include:* | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| *Methadone* | *61 (73.5)* | *22 (26.5)* | *83* | *42.6* | *84 (71.8)* | *33 (28.2)* | *117* | *56.5* | *108 (72.0)* | *42 (28.0)* | *150* | *64.4* | *144 (81.8)* | *32 (18.2)* | *176* | *62.2* | *141 (77.9)* | *40 (22.1)* | *181* | *62.0* | *135 (69.2)* | *60 (30.8)* | *195* | *64.8* | *135 (67.5)* | *65 (32.5)* | *200* | *66.2* |
| *Codeine* | *12 (57.1)* | *9 (42.9)* | *21* | *10.8* | *13 (50.0)* | *13 (50.0)* | *26* | *12.6* | *13 (40.6)* | *19 (59.4)* | *32* | *13.7* | *25 (54.3)* | *21 (45.7)* | *46* | *16.3* | *23 (57.5)* | *17 (42.5)* | *40* | *13.7* | *22 (57.9)* | *16 (42.1)* | *38* | *12.6* | *11 (29.7)* | *26 (70.3)* | *37* | *12.3* |
| *Tramadol* | *5 (38.5)* | *8 (61.5)* | *13* | *6.7* | *8 (33.3)* | *16 (66.7)* | *24* | *11.6* | *13 (61.9)* | *8 (38.1)* | *21* | *9.0* | *19 (52.8)* | *17 (47.2)* | *36* | *12.7* | *28 (53.8)* | *24 (46.2)* | *52* | *17.8* | *23 (48.9)* | *24 (51.1)* | *47* | *15.6* | *26 (60.5)* | *17 (39.5)* | *43* | *14.2* |
| *Fentanyl** | *~* | *0* | *~* | | *0* | *0* | *0* | | *~* | *0* | *~* | | *0* | *~* | *~* | | *~* | *~* | *~* | | *6 (54.5)* | *5 (45.5)* | *11* | *3.7* | *9 (64.3)* | *5 (35.7)* | *14* | *4.6* |
| *Rx opioids involved in polydrug poisoning deaths (67.5% involved benzodiazepines)* | 86 (61.9) | 53 (38.1) | 139 | 71.3 | 95 (65.5) | 50 (34.5) | 145 | 70.0 | 125 (68.3) | 58 (31.7) | 183 | 78.5 | 173 (73.3) | 63 (26.7) | 236 | 83.4 | 174 (70.2) | 74 (29.8) | 248 | 84.9 | 173 (63.4) | 100 (36.6) | 273 | 90.7 | 163 (62.9) | 96 (37.1) | 259 | 85.8 |
| **Benzodiazepines** | 78 (60.5) | 51 (39.5) | 129 | 22.8 | 120 (63.8) | 68 (36.2) | 188 | 26.4 | 160 (73.7) | 57 (26.3) | 217 | 28.6 | 198 (72.5) | 75 (27.5) | 273 | 38.1 | 209 (71.8) | 82 (28.2) | 291 | 38.4 | 212 (67.9) | 100 (32.1) | 312 | 42.2 | 197 (68.4) | 91 (31.6) | 288 | 38.7 |
| *Of which the main drugs involved include:* | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| *Diazepam* | *48 (66.7)* | *24 (33.3)* | *72* | *55.8* | *81 (64.3)* | *45 (35.7)* | *126* | *67.0* | *110 (75.3)* | *36 (24.7)* | *146* | *67.3* | *153 (76.1)* | *48 (23.9)* | *201* | *73.6* | *160 (78.0)* | *45 (22.0)* | *205* | *70.4* | *165 (72.4)* | *63 (27.6)* | *228* | *73.1* | *135 (71.4)* | *54 (28.6)* | *189* | *65.6* |
| *Flurazepam* | *16 (51.6)* | *15 (48.4)* | *31* | *24.0* | *24 (54.5)* | *20 (45.5)* | *44* | *23.4* | *32 (71.1)* | *13 (28.9)* | *45* | *20.7* | *51 (66.2)* | *26 (33.8)* | *77* | *28.2* | *46 (64.8)* | *25 (35.2)* | *71* | *24.4* | *44 (62.0)* | *27 (38.0)* | *71* | *22.8* | *52 (67.5)* | *25 (32.5)* | *77* | *26.7* |
| *Alprazolam* | *~* | *~* | *~* | | *5 (100.0)* | *0* | *5* | | *~* | *~* | *5* | | *29 (65.9)* | *15 (34.1)* | *44* | | *46 (74.2)* | *16 (25.8)* | *62* | | *58 (61.7)* | *36 (38.3)* | *94* | | *79 (71.8)* | *31 (28.2)* | *110* | |
| *Benzodiazepines involved in polydrug poisoning deaths (60% involved Rx Opioids)* | 75 (60.0) | 50 (40.0) | 125 | 96.9 | 116 (63.7) | 66 (36.3) | 182 | 96.8 | 159 (73.6) | 57 (26.4) | 216 | 99.5 | 196 (72.6) | 74 (27.4) | 270 | 98.9 | 207 (72.1) | 80 (27.9) | 287 | 98.6 | 208 (68.0) | 98 (32.0) | 306 | 98.1 | 197 (68.4) | 91 (31.6) | 288 | 100.0 |
| **Antidepressants** | 42 (45.7) | 50 (54.3) | 92 | 16.3 | 46 (54.1) | 39 (45.9) | 85 | 11.9 | 68 (50.4) | 67 (49.6) | 135 | 17.8 | 79 (53.7) | 68 (46.3) | 147 | 20.5 | 84 (46.9) | 95 (53.1) | 179 | 23.6 | 93 (49.5) | 95 (50.5) | 188 | 25.4 | 88 (52.7) | 79 (47.3) | 167 | 22.4 |
| *Of which the main drugs involved include:* | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| *Citalopram* | *11 (40.7)* | *16 (59.3)* | *27* | *29.3* | *10 (47.6)* | *11 (52.4)* | *21* | *24.7* | *17 (42.5)* | *23 (57.5)* | *40* | *29.6* | *32 (61.5)* | *20 (38.5)* | *52* | *35.4* | *21 (53.8)* | *18 (46.2)* | *39* | *21.8* | *22 (52.4)* | *20 (47.6)* | *42* | *22.3* | *16 (50.0)* | *16 (50.0)* | *32* | *19.2* |
| *Amitriptyline* | *14 (63.6)* | *8 (36.4)* | *22* | *23.9* | *8 (61.5)* | *5 (38.5)* | *13* | *15.3* | *14 (41.2)* | *20 (58.8)* | *34* | *25.2* | *11 (47.8)* | *12 (52.2)* | *23* | *15.6* | *12 (30.8)* | *27 (69.2)* | *39* | *21.8* | *22 (47.8)* | *24 (52.2)* | *46* | *24.5* | *21 (58.3)* | *15 (41.7)* | *36* | *21.6* |
| *Venlafaxine* | *6 (50.0)* | *6 (50.0)* | *12* | *13.0* | *7* | *~* | *9* | *10.6* | *8 (57.1)* | *6 (42.9)* | *14* | *10.4* | *12 (52.2)* | *11 (47.8)* | *23* | *15.6* | *6 (33.3)* | *12 (66.7)* | *18* | *10.1* | *7 (30.4)* | *16 (69.6)* | *23* | *12.2* | *9 (52.9)* | *8 (47.1)* | *17* | *10.2* |
| *Antidepressants involved in polydrug poisoning deaths (61% involved benzodiazepines)* | 34 (44.2) | 43 (55.8) | 77 | 52.4 | 38 (53.5) | 33 (46.5) | 71 | 83.5 | 57 (51.8) | 53 (48.2) | 110 | 81.5 | 74 (56.1) | 58 (43.9) | 132 | 89.8 | 77 (49.0) | 80 (51.0) | 157 | 87.7 | 85 (50.0) | 85 (50.0) | 170 | 90.4 | 79 (53.0) | 70 (47.0) | 149 | 89.2 |
| **Alcohol** | 150 (62.2) | 91 (37.8) | 241 | 42.6 | 192 (67.1) | 94 (32.9) | 286 | 40.2 | 203 (67.7) | 97 (32.3) | 300 | 39.6 | 216 (73.7) | 77 (26.3) | 293 | 40.9 | 202 (74.3) | 70 (25.7) | 272 | 35.9 | 165 (70.5) | 69 (29.5) | 234 | 31.6 | 186 (70.7) | 77 (29.3) | 263 | 35.3 |
| *Alcohol involved in polydrug poisoning deaths (30% involved benzodiazepines)* | *75 (58.1)* | *54 (41.9)* | *129* | *53.5* | *98 (67.6)* | *47 (32.4)* | *145* | *50.7* | *109 (69.9)* | *47 (30.1)* | *156* | *52.0* | *114 (75.0)* | *38 (25.0)* | *152* | *51.9* | *94 (69.6)* | *41 (30.4)* | *135* | *49.6* | *95 (70.4)* | *40 (29.6)* | *135* | *57.7* | *100 (74.1)* | *45 (33.3)* | *135* | *51.3* |
| **Cocaine** | 48 (87.3) | 7 (12.7) | 55 | 9.7 | 99 (83.2) | 20 (16.8) | 119 | 16.7 | 88 (77.2) | 26 (22.8) | 114 | 15.0 | 41 (91.1) | ~ | 45 | 6.3 | 50 (86.2) | 8 (13.8) | 58 | 7.7 | 71 (80.7) | 17 (19.3) | 88 | 11.9 | 71 (74.7) | 24 (25.3) | 95 | 12.8 |
| *Cocaine involved in polydrug poisoning deaths (54% involved benzodiazepines)* | 29 (82.9) | 6 (17.1) | 35 | 63.6 | 57 (83.8) | 11 (16.2) | 68 | 57.1 | 73 (77.7) | 21 (22.3) | 94 | 82.5 | 38 (90.5) | ~ | 42 | 93.3 | 48 (85.7) | 8 (14.3) | 56 | 96.6 | 66 (80.5) | 16 (19.5) | 82 | 93.2 | 59 (72.8) | 22 (27.2) | 81 | 85.3 |
| **Heroin** | 69 (90.9) | 7 (9.2) | 76 | 13.4 | 135 (90.6) | 14 (9.4) | 149 | 20.9 | 178 (86.8) | 27 (13.2) | 205 | 27.0 | 120 (88.2) | 16 (11.8) | 136 | 19.0 | 139 (91.4) | 13 (8.6) | 152 | 20.1 | 154 (85.1) | 27 (14.9) | 181 | 24.5 | 129 (85.4) | 22 (14.6) | 151 | 20.3 |
| *Heroin involved in polydrug poisoning deaths (65% involved benzodiazepines)* | *39 (95.1)* | *~* | *41* | *53.9* | *85 (87.6)* | *12 (12.4)* | *97* | *65.1* | *117 (83.0)* | *24 (17.0)* | *141* | *68.8* | *80 (86.0)* | *13 (14.0)* | *93* | *68.4* | *109 (91.6)* | *10 (8.4)* | *119* | *78.3* | *123 (84.8)* | *22 (15.2)* | *145* | *80.1* | *109 (86.5)* | *17 (13.5)* | *126* | *83.4* |

~ = value less than 5

* Although fentanyl is not one of the main prescription opioid drugs involved in drug poisoning deaths in Ireland, data displayed for information purposes

¥ This is a multiresponse analysis taking into account up to six drug implicated in any one death, therefore individual rows will not equal totals.

**STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional studies***

| Section/Topic | Item # | Recommendation | Reported on page # |
|---|---|---|---|
| **Title and abstract** | 1 | (*a*) Indicate the study's design with a commonly used term in the title or the abstract | 1 |
| | | (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found | 2 |
| **Introduction** | | | |
| Background/rationale | 2 | Explain the scientific background and rationale for the investigation being reported | 4 |
| Objectives | 3 | State specific objectives, including any prespecified hypotheses | 5 |
| **Methods** | | | |
| Study design | 4 | Present key elements of study design early in the paper | 5-6 |
| Setting | 5 | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection | 6 |
| Participants | 6 | (*a*) Give the eligibility criteria, and the sources and methods of selection of participants | 6-10 |
| Variables | 7 | Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable | 8 |
| Data sources/ measurement | 8* | For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group | 6-10 |
| Bias | 9 | Describe any efforts to address potential sources of bias | |
| Study size | 10 | Explain how the study size was arrived at | |
| Quantitative variables | 11 | Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why | 6-10 |
| Statistical methods | 12 | (*a*) Describe all statistical methods, including those used to control for confounding | 8-10 |
| | | (*b*) Describe any methods used to examine subgroups and interactions | 9-10 |
| | | (*c*) Explain how missing data were addressed | |
| | | (*d*) If applicable, describe analytical methods taking account of sampling strategy | |
| | | (*e*) Describe any sensitivity analyses | |
| **Results** | | | 10 |

| | | | |
|---|---|---|---|
| Participants | 13* | (a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed | 10 |
| | | (b) Give reasons for non-participation at each stage | |
| | | (c) Consider use of a flow diagram | |
| Descriptive data | 14* | (a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders | 10-15 |
| | | (b) Indicate number of participants with missing data for each variable of interest | |
| Outcome data | 15* | Report numbers of outcome events or summary measures | 10-15 |
| Main results | 16 | (*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included | 10-16 |
| | | (*b*) Report category boundaries when continuous variables were categorized | |
| | | (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period | |
| Other analyses | 17 | Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses | 10-16 |
| **Discussion** | | | |
| Key results | 18 | Summarise key results with reference to study objectives | 16-20 |
| Limitations | 19 | Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias | 24-25 |
| Interpretation | 20 | Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence | 16-25 |
| Generalisability | 21 | Discuss the generalisability (external validity) of the study results | 16-23 |
| **Other information** | | | |
| Funding | 22 | Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based | 25 |

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

# Trends in drug poisoning deaths, by sex, in Ireland: a repeated cross-sectional study from 2004 to 2017

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| | |

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# Trends in drug poisoning deaths, by sex, in Ireland: a repeated cross-sectional study from 2004 to 2017

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# Trends in drug poisoning deaths, by sex, in Ireland: a repeated cross-sectional study from 2004 to 2017


## Abstract

**Objective** Examine sex differences in age-standardised rates (ASR) of overall and drug-specific drug poisoning deaths, in Ireland between 2004 and 2017.

**Design** Repeated cross-sectional study.

**Setting** Drug poisoning deaths in Ireland.

**Participants** National Drug-Related Deaths Index (NDRDI) and pharmacy claims database (PCRS-GMS) data, 2004 to 2017.

**Outcome measures** Primary outcome: trends in drug poisoning death rates by sex. Secondary outcomes: trends in drug poisoning death rates involving (1) any CNS depressants (2) ≥ 2 CNS depressants, and (3) individual drug classes (e.g. prescription opioids, benzodiazepines, antidepressants, alcohol, cocaine, and heroin) by sex. Joinpoint Regression was used to examine trends, stratified by sex, in the ASR of drug poisoning deaths (2004 to 2017), change points over time and average annual percentage changes (AAPCs) with 95% confidence intervals (CI).

**Results** Increased ASR for all drug poisoning deaths from 6.86 (95% CI 6.01-7.72) per 100,000 in 2004 to 8.08 (95% CI 7.25-8.91) per 100,000 in 2017, was mainly driven by increasing deaths among men (AAPC 2.6% [95% CI, 0.2 - 5.1]), with no significant change observed among women. Deaths involving ≥ 2 CNS depressants increased for both men (AAPC 5.6% [95% CI, 2.4 - 8.8]) and women (AAPC 4.0% [95% CI, 1.1 - 6.9]). Drugs with the highest significant AAPC increases for men were cocaine (7.7% [(95% CI, 2.2 - 13.6]), benzodiazepines (7.2% [(95% CI, 2.9 - 11.6]), antidepressants (6.1% [(95% CI, 2.4 - 10.0])

and prescription opioids (3.5% [(95% CI, 1.6 - 5.5]). For women, the highest AAPC was for antidepressants (4.2% [(95% CI, 0.2 - 8.3]), benzodiazepines (3.3% [(95% CI, 0.1 - 6.5]) and prescription opioids (3.0% [(95% CI, 0.7 - 5.3]).

**Conclusion** Drugs implicated in drug poisoning deaths vary by sex. Policy response should include prescription monitoring programmes, and practical harm reduction information on polydrug use, especially CNS depressant drugs.

**Key words** Drug; poisoning; death; men; women; sex; gender.

## Article Summary

### *Strengths and limitations of this study:*

- The NDRDI incorporates national data from four different sources, providing more robust and complete data on drug poisoning deaths.
- Use of mortality data in addition to prescription data enabled assessment of the relationship between trends in prescribing and poisoning deaths involving specific drugs.
- Limitations of this study include the reliance on individual Coroners to implicate specific drugs in poisoning deaths, which can be challenging when multiple drugs are present on a toxicology report.
- Information on whether the drugs were prescribed for the individual is frequently not available in the sources of data, which limits the assessment of illicit use of these drugs and the impact of illicit drugs on these deaths.
- Lack of data on private prescription drugs dispensed, stratified by sex, limits analysis to those dispensed through the government assisted drug payment scheme.

## Introduction

Drug poisonings are a leading cause of avoidable death worldwide, with rates increasing globally. National trends from the United States (U.S.) show that drug poisoning deaths have increased rapidly in recent years, with a 15% increase per year between 2013 and 2017.(1) During this period drug poisoning death rates increased in most U.S. states, primarily due to synthetic opioids.(2) Drug poisoning deaths involving psychostimulants, especially cocaine, have also increased in the U.S.(3, 4) Accidental drug poisonings are predicted to be a leading cause of premature deaths in the U.S. over the next decade, especially among women.(5) Drug poisoning deaths have also increased in Australia since 2006, with opioids being the most common drug group involved in these deaths.(6)

Similar patterns have been observed across Europe. For example, the number of drug poisoning deaths recorded in England and Scotland in 2017 was the highest ever recorded, with opioid-related deaths representing the leading cause of these deaths.(7) The European Monitoring Centre of Drugs and Drug Addiction (EMCDDA) also reported an increase in drug poisoning deaths between 2012 and 2018 in Europe, increasing from an estimated 17 deaths per million population aged 15-64 years in 2012,(8) to 22.6 deaths per million population aged 15-64 years in 2018.(9) Opioids (both licit and illicit), commonly heroin, are involved in approximately 8 out of every 10 drug poisoning deaths reported in Europe. (9) However, post-mortem toxicology analyses of poisoning deaths suggest that multiple drug toxicity is implicated in most deaths.(9)

While sex differences in drug poisoning deaths have emerged in recent years,(10) most of the available evidence fails to account for variation by sex regarding drugs involved.(11) Consequently, as drug poisoning deaths are dominated by men, specific circumstances associated with drug poisoning deaths among women may be masked by combining trends for men and women. For example, in the U.S., a higher risk of drug

poisoning death among young men relative to young women has been reported to be attributed to heroin and synthetic drugs.(10) In contrast, in both the U.S. and Scotland, risk of drug poisoning deaths among older women were attributed to prescription opioids, antidepressants,(12, 13) and unspecified drugs.(10) Many drug poisoning deaths involve a fatal cocktail of CNS depressant drugs.(14), (15) Sex-specific differences in pharmacokinetics for CNS depressant drugs such as opioids,(16) pregabalin and benzodiazepines,(17) suggest that these drugs may be impacting more on polydrug poisoning deaths among women.

Furthermore, although the absolute number of drug poisoning deaths are higher in men, epidemiological trends in Europe and the U.S. suggest the rate of drug poisoning deaths among women is increasing at a higher rate relative to men,(9, 18, 19) especially in relation to intentional drug poisoning deaths.(20)

The aim of this study is to examine sex differences in age-standardised rates of overall drug poisoning deaths, and drug poisoning deaths involving (1) any CNS depressants; (2) ≥ 2 CNS depressants; (3) individual drug classes (e.g. prescription opioids, benzodiazepines, antidepressants, alcohol, cocaine, and heroin) in Ireland between 2004 and 2017.

This study also examines the association between dispensing rates of prescribed medications commonly implicated in drug poisoning deaths (specifically benzodiazepines and antidepressants), and drug poisoning deaths involving these agents.

## Methods

The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist for cross-sectional studies,(21) was used as a guide to structure this repeated cross-sectional study. The study was approved by the Royal College of Surgeons in Ireland Research Ethics Committee on 1st May 2018 REC 1542.

## *Patient and Public Involvement*

No patients were involved in the design or conduct of the study.

## *Data sources*

*Drug poisoning deaths*

Design: Repeated cross-sectional study.

This study includes anonymized individual level data on all drug poisoning deaths in Ireland as recorded by the National Drug-Related Deaths Index (NDRDI) for years of death 2004 to 2017 inclusive. The NDRDI is an epidemiological database which records all poisoning deaths by drugs and/or alcohol.(22) It follows the EMCDDA standard protocol to collect data on drug-related deaths.(23) To ensure completeness, data from several sources are collected and cross-checked to avoid duplication. Coronial files are the main data source for the NDRDI. Coronial data are collected for the purpose of death investigation, not primarily for research. However, coronial data have been recognised as a rich source of data for monitoring drug poisoning deaths.(24) Other NDRDI data sources include: the General Mortality Register (via the Central Statistics Office (CSO)), acute hospitals data (via the Hospital In-patient Enquiry System [HIPE]) and the national opioid agonist treatment (OAT) register (via the Central Treatment List (CTL)). Further details on the NDRDI methodology can be found elsewhere.(22) The methodology for collecting poisoning deaths did not change over the study period.

The NDRDI's definition of a poisoning death is a death directly due to the toxic effect of one or more drugs (including alcohol) on the body, as recorded by the Coroner on the certificate of death registration and/or the record of verdict. Up to six drugs implicated in drug poisoning deaths by the Coroner can be included in the NDRDI. Data on deaths which included specific drugs and drug groups, including opioids, benzodiazepines, antidepressants, Z-drugs

(zopiclone and zolpidem), pregabalin, alcohol and cocaine, were extracted from the NDRDI for this study. These are the main drugs implicated in poisoning deaths in Ireland.(15)

*Pharmacy claims data*

Aggregate level (by age, sex, year, and drug class) pharmacy claims data on prescription drugs, including benzodiazepines and antidepressants, were available from the Irish Health Service Executive (HSE) Primary Care Reimbursement Services (PCRS). This included only those with full eligibility for the General Medical Services (GMS) scheme at any time during 2004 to 2017 inclusive. Eligibility for the GMS is mainly through means-testing and age; therefore, it over-represents the more socially deprived, younger, and older aged populations in Ireland.

The HSE PCRS-GMS pharmacy claims database funds the majority of pharmaceutical expenditure.(25) It contains details of all prescription medications dispensed to GMS eligible patients in primary care but does not include data on private prescriptions dispensed or hospital prescriptions. However, the PCRS-GMS pharmacy claims database represents the single largest pharmacy claims dataset in Ireland. All claims are coded using the WHO's Anatomical Therapeutic Chemical (ATC) classification. The PCRS-GMS database contains basic demographic information including age, sex, and region of residence.(25) As of 2015, almost 40% of the Irish population were covered by the GMS scheme.(25)

Data on all eligible individuals ≥16 years of age who were prescribed benzodiazepines (N05CD, N05BA or N03AE01) and/or antidepressants (N06AA, N06AB, N06AF, N06AG or N06AX), were also extracted from the PCRS-GMS database and included in the study. While the PCRS-GMS database records prescription opioids, it does not record methadone or buprenorphine prescriptions for the treatment of opioid dependency. Therefore, the available data on opioids was considered incomplete for the purpose of this study.

### *Study variables*

The primary outcome was drug poisoning deaths, defined as a death directly due to the toxic effect of one or more drugs (including alcohol) on the body, by sex. The secondary outcomes of interest were drug poisoning deaths involving: (1) any CNS depressant drugs, (2) ≥ 2 CNS depressants drugs, (3) individual drug classes (prescribed opioids, benzodiazepines, antidepressants, alcohol, cocaine, and heroin) by sex. If multiple drugs were implicated in an individual death, then this death can be included in multiple drug categories.

For poisoning deaths involving CNS depressant drugs, any death involving at least one drug from the following drug categories: opioids (ICD 10 codes T40.2, T40.3, T40.4 and T40.6), benzodiazepines (ICD 10 code T42.4), alcohol (ICD 10 code T51), pregabalin and/or Z-drugs (ICD 10 code T42.6 with specific individual NDRDI drug codes for pregabalin, zolpidem and zopiclone identified) were combined into deaths due to 'any CNS depressant drug'. Sex, year of death and age groups (15-29, 30-44, 45-59 and ≥60 years) were also included.

### *Statistical analysis*

All analyses of trends were examined overall and separately for men and women.

*Drug poisoning deaths*

Irish general population estimates were extracted from the CSO for calculation of rates of drug poisoning deaths per 100,000 population.(26) For prescription rates the GMS eligible population for those aged 16 years and older was extracted from the PCRS annual reports.(27) The European Standard Population (ESP) was used to calculate age-standardised rates (ASR).(28)

Trends in age-standardised mortality rates (ASMR) for all drug poisoning deaths and the specific drug groups mentioned above were examined by sex while adjusting for age. Mortality rates for each year of the study period were calculated per 100,000 of the general population based on national census and projected population figures,(26) standardised to the European Standard Population (ESP).(28) Rate ratios of ASMR for men compared to women were calculated and 95% confidence intervals (CI) computed using the delta method for the variance. Joinpoint Regression Program version 4.8.0.1(29) was used to examine any changes in trends in age-standardised rates from 2004 to 2017, expressed as annual percentage changes (APCs), with a summary of the overall trend expressed as an average annual percentage change (AAPC). The AAPC is a summary measure which describes the average of the APCs over time. Joinpoint regression detects if there are any statistically significant trend changes in, the overall drug poisoning death rates over time, drug poisoning death rates involving any CNS depressant drugs, ≥ 2 CNS depressants drugs and for each of the drug classes described. Time periods for change in APCs were permitted to vary according to whether or not there were statistically significant change points. A change point is a specific time point where a statistically significant trend change occurred (or a change in the APC). The APCs and the overall AAPCs are presented in the tables with results displayed by sex.

*Association with prescribing patterns*

Age-standardised prescription rates (ASPR) per 1,000 of GMS eligible population for each calendar year were standardised using the relevant age categories from the ESP.

Ecological analysis of the aggregated data, using annual age-standardised rates for drug poisoning deaths and prescription data, was performed using linear regression to examine the relationship (beta regression coefficient, 95% CI) between trends in age

standardised prescription rates for benzodiazepines and antidepressants. Analyses were stratified by sex.

Statistical significance at $p < 0.05$ is assumed. Data were analysed using Joinpoint Regression Program (Version 4.8.0.1 National Cancer Institute, U.S.), and SPSS version 22 (IBM SPSS Statistics for Windows, v.22.0. Armonk, NY: IBM Corp.).

## Results

### *All drug poisoning deaths*

For the study period 2004 to 2017 there were 4,993 drug poisoning deaths recorded in Ireland. In 2004 there were 266 drug poisoning deaths (175 [66%] men: 91 [34%] women), representing an ASMR of 6.86 deaths per 100,000 (8.5 ASMR per 100,000 men and 5.0 ASMR per 100,000 women). By 2017 there were 376 drug poisoning deaths, an increase of 41.4%, (263 [70%] men: 113 [30%] women) representing an ASMR of 8.08 per 100,000 (11.5 ASMR per 100,000 men and 4.8 ASMR per 100,000 women). The rate of all drug poisoning deaths among men from 2004 to 2017 increased at an AAPC of 2.6% (95% CI, 0.2 - 5.1) (Table 1). However, there was no significant change among women for the same period (Table 2). Joinpoint regression analysis identified an accelerated increase in drug poisoning deaths among men in earlier years (2004 – 2007) with no significant change in the latter years 2007 – 2017 (Table 1).

The ASMR for 2004 and 2017 by any CNS depressant drugs, ≥ 2 CNS depressant drugs, individual drug classes and individual drugs, stratified by sex are also presented in Tables 1 (men) and 2 (women).

### *CNS depressant drugs*

The rate of drug poisoning deaths involving any CNS depressant drugs increased from an ASMR of 5.61 deaths per 100,000 in 2004 to an ASMR of 6.38 per 100,000 in 2017

(Table 3). There was an AAPC increase of 2.2% (95% CI, 0.3 – 4.3) for men with an accelerated increase noted for the period 2004 to 2008. However, when drug poisoning deaths involved ≥ 2 CNS depressant drugs, men showed a higher AAPC at 5.6% (95% CI, 2.4 – 8.8) (Table 1).

For women who died of drug poisoning deaths involving any CNS depressant drugs, no significant AAPC was observed. However, when ≥ 2 CNS depressant drugs were involved in the death, there was an AAPC of 4% (95% CI, 1.1 – 6.9) (Table 2).

Benzodiazepines were the main drug group implicated in all (men and women combined) drug poisoning deaths involving ≥ 2 CNS depressant drugs, implicated in 76% of these deaths.

### *Prescription Opioids*

All drug poisoning deaths involving prescription opioids, of which 61% consisted of methadone, have increased over time (Table 3) with similar AAPC for both men (3.5% [95% CI, 1.6 - 5.5]) and women (3.0% [95% CI, 0.7 - 5.3]) with no change points, indicating no change in trend(s) within the reporting period noted (Tables 1 & 2). Overall, 43% (n = 477) of deaths involving methadone were among people with a history of opioid dependence and registered on the national opioid agonist treatment (OAT) register, increasing from 35% (n = 14) in 2004 to 52% (n = 49) in 2017. Although fewer women are in receipt of OAT relative to men, almost two in three women (n = 185, 63%) who had methadone implicated in their death were registered on the OAT register. In contrast, just over one in three (n = 292, 36%) men, where methadone was implicated in their poisoning death, were registered on the national opioid agonist treatment (OAT) register. However, it must be noted that clients can remain on the OAT register up to 30 days after dropping out of treatment. Therefore, it is unclear whether these deaths occurred while a person was on or off treatment.

### *Benzodiazepines*

The rate of drug poisoning deaths involving benzodiazepines increased over the observation period at an AAPC of 7.2% (95% CI, 2.9 – 11.6) among men (Table 1) and 3.3% (95% CI, 0.1 – 6.5) among women (Table 2) with no change points, indicating no change in trend(s) within the reporting period, observed for either men or women (Table 1 & Table 2). Diazepam was the main benzodiazepine drug involved in these deaths. However, there has been a substantial increase in the number of drug poisoning deaths involving alprazolam in the latter years (supplementary file 1: Table 1) for both men and women. In 2004 alprazolam was involved in less than five deaths, rising to 63 deaths in 2017 with the majority among men (men: n = 47, 75%; women: n = 16, 25%).

For benzodiazepines, a negative relationship was observed between prescribing data and drug poisoning deaths for both men (β = -0.067, [95% CI -0.116, -0.018], p = 0.012) and women (β = -0.016, [95% CI -0.031, 0.000], p = 0.044) for the period 2004 to 2017 (Figure 1). However this relationship was not statistically significant for women.

Insert Figure 1

### *Antidepressants*

For both men (6.1% [95% CI, 2.4 – 10.0]) and women (4.2% [95% CI, 0.2 – 8.3]) there was a significant increase in the AAPC rates for drug poisoning deaths involving antidepressants (Tables 1 & Table 2). There were no change points, indicating no change in trend(s) within the reporting period observed (Tables 1 & Table 2). Although the ASMR for women in 2017 (1.40 per 100,000) was lower than the rate in 2004 (1.71 per 100,000), the yearly rates fluctuated during the reported period with an overall upward trend. This did not result in any significant change points.

For antidepressants, a positive relationship between prescription data and drug poisoning data was observed for both men (β = 0.013, [95% CI 0.003, 0.022], p = 0.011) and women (β = 0.006, [95% CI 0.000, 0.012], p = 0.045) (Figure 2). The age standardised rate of antidepressant items dispensed per 1000 of the GMS population increased over the study period for both men (from 153.1 per 1000 in 2004 to 218.6 per 1000 in 2017) and women (from 232.0 per 1000 in 2004 to 336.3 per 1000 in 2017).

Insert Figure 2

### *Alcohol*

The rate for women who died of drug poisoning deaths involving alcohol decreased with an AAPC decrease of 4.0% (95% CI, -5.8 – -2.1) between 2004 and 2017 (Table 2). There was no statistically significant AAPC in rates for men in the same period (Table 1). No significant change points, indicating no change in trend(s) within the reporting period, were observed for men or women. Over half of all drug poisoning deaths involving alcohol were polydrug poisoning deaths (n =1889, 52.8%) with similar percentages for men (n = 685, 52.1%) and women (n = 312, 54.3%) (supplementary file 1: Table 1). Other CNS depressant drugs were implicated in almost a third (n = 575, 30.4%) of polydrug poisoning deaths involving alcohol. Benzodiazepines were the main other CNS depressant drug group involved in alcohol polydrug poisoning deaths; implicated in one-in-three drug poisoning deaths involving alcohol (n = 563, 29.8%).

### *Cocaine*

Drug poisoning deaths involving cocaine fluctuated over the study period. For men, an accelerated increase was observed during the periods 2004 to 2006 and 2010 to 2017, with a significant decrease during the intervening period 2006 to 2010, giving an overall AAPC increase of 7.7% (95% CI, 2.2 – 13.6) (Table 1). Accelerated increases were also identified

among women in the periods 2004 to 2008 and 2011 to 2017, but no significant AAPC was observed among women (Table 2). Although there is a higher incidence of cocaine-related drug poisoning deaths among men relative to women, the gap between men and women is narrowing, with the ASMR ratio of men to women decreasing from 11.7 in 2004 to 6.0 in 2017 (Table 3).

### *Heroin*

No trend change, for either sex, was observed for drug poisoning deaths involving heroin over the study period (Tables 1 & Table 2). While the incidence of heroin drug poisoning deaths is low among women relative to men, the gap between men and women is reducing with the ASMR ratio of men to women decreasing from 11.7 in 2004 to 6.0 in 2017 (Table 3).

**Table 1: Age-standardised rates (ASR) (standardised to the European Standard Population) of drug poisoning deaths, per 100,000 of the general population, with APCs identified for specific change points and overall AAPCs, 2004 to 2017, among men in Ireland**

| Men | | | | | |
|---|---|---|---|---|---|
| | | †ASR per 100,000 population at change points identified | | | |
| **Drug group** | **Period** | **Start** | **End** | **APC (95% CI) %** | **AAPC (95% CI) %** |
| All drug poisoning deaths | 2004-2007 | 8.51 | 11.50 | 13.2 (1.6 to 26.1)*** | |
| | 2007-2017 | 11.50 | 11.19 | -0.3 (-1.9 to 1.2) | |
| | 2004-2017 | 8.51 | 11.19 | | 2.6 (0.2 to 5.1)*** |
| Any CNS depressant drug | 2004-2008 | 6.91 | 9.75 | 10.1 (3.3 to 17.3)*** | |
| | 2008-2017 | 9.75 | 8.57 | -1.1 (-2.7 to 0.6) | |
| | 2004-2017 | 6.91 | 8.57 | | 2.2 (0.3 to 4.3)*** |
| 2 or more CNS depressant drugs | 2004-2011 | 2.29 | 5.67 | 10.8 (5.9 to 16.0)*** | |
| | 2011-2017 | 5.67 | 4.95 | -0.2 (-5.4 to 5.3) | |
| | 2004-2017 | 2.29 | 4.95 | | 5.6 (2.4 to 8.8)*** |
| Prescription opioids | 2004-2017 | 2.76 | 3.96 | | 3.5 (1.6 to 5.5)*** |
| Benzodiazepines | 2004-2017 | 1.56 | 3.96 | | 7.2 (2.9 to 11.6)*** |
| Antidepressants | 2004-2017 | 0.70 | 1.50 | | 6.1 (2.4 to 10.0)*** |
| Alcohol | 2004-2017 | 4.12 | 3.83 | | -0.9 (-3.2 to 1.4) |
| Cocaine | 2004-2006 | 0.64 | 2.19 | 107.3 (56 to 175.6)*** | |
| | 2006-2010 | 2.19 | 0.64 | -25 (-35.1 to -13.3)*** | |
| | 2010-2017 | 0.64 | 1.58 | 9.9 (5.6 to 14.3)*** | |
| | 2004-2017 | 0.64 | 1.58 | | 7.7 (2.2 to 13.6)*** |
| Heroin | 2004-2006 | 0.61 | 2.70 | 83.4 (-33.7 to 407.7) | |
| | 2006-2017 | 2.70 | 2.64 | -1.1 (-4.5 to 2.5) | |
| | 2004-2017 | 0.61 | 2.64 | | 8.8 (-5.2 to 24.9) |

Variables significant at ***p < 0.001, ** p < 0.01, * p < 0.05.
APC = Annual percentage change. The APC was reported for time periods where a statistically significant trend change occurred
AAPC = Average annual percentage change
Change point = a specific time period where a statistically significant trend change occurred
†ASR per 100,000 population at the start and end of the change points identified and at the start and end of the study period

**Table 2: Age-standardised rates (ASR) (standardised to the European Standard Population) of drug poisoning deaths, per 100,000 of the general population, with APCs identified for specific change points and overall AAPCs, 2004 to 2017, among women in Ireland**

| Women | | | | | |
|---|---|---|---|---|---|
| | | †ASR per 100,000 population at change points identified | | | |
| **Drug group** | **Period** | **Start** | **End** | **APC (95% CI) %** | **AAPC (95% CI) %** |

| | | | | | |
|---|---|---|---|---|---|
| All drug poisoning deaths | 2004-2017 | 4.99 | 4.84 | | -0.5 (-2.2 to 1.2) |
| Any CNS depressant drug | 2004-2012 | 4.20 | 3.21 | -0.9 (-5.1 to 3.4) | |
| | 2012-2017 | 3.21 | 3.98 | 1.5 (-6.3 to 9.8) | |
| | 2004-2017 | 4.20 | 3.98 | | -0.0 (-3.4 to 3.5) |
| 2 or more CNS depressant drugs | 2004-2017 | 2.08 | 2.11 | | 4.0 (1.1 to 6.9)*** |
| Prescription opioids | 2004-2017 | 1.54 | 2.02 | | 3.0 (0.7 to 5.3)*** |
| Benzodiazepines | 2004-2017 | 1.70 | 1.67 | | 3.3 (0.1 to 6.5)*** |
| Antidepressants | 2004-2017 | 1.71 | 1.40 | | 4.2 (0.2 to 8.3)*** |
| Alcohol | 2004-2017 | 2.72 | 1.65 | | -4.0 (-5.8 to -2.1)*** |
| Cocaine | 2004-2008 | 0.08 | 0.45 | 61.1 (14.0 to 127.6)*** | |
| | 2008-2011 | 0.45 | 0.04 | -56.6 (-84.1 to 18.6) | |
| | 2011-2017 | 0.04 | 0.58 | 53.8 (26 to 87.8)*** | |
| | 2004-2017 | 0.08 | 0.58 | | 16.5 (-6.3 to 44.8) |
| Heroin | 2004-2017 | 0.09 | 0.47 | | 7.0 (-0.2 to 14.6) |

Variables significant at ***p < 0.001, ** p < 0.01, * p < 0.05.
APC = Annual percentage change. The APC was reported for time periods where a statistically significant trend change occurred
APC = Average annual percentage change
Change point = a specific time period where a statistically significant trend change occurred
†ASR per 100,000 population at the start and end of the change points identified and at the start and end of the study period

**Table 3: Age-standardised rates (standardised to the European Standard Population) of drug poisoning deaths, per 100,000 of the general population, 2004 to 2017, among all drug poisoning deaths in Ireland and ratio of men to women.**

| Total drug poisoning deaths | | | | |
|---|---|---|---|---|
| | Age-standardised rates per 100,000 population (95% CI) | | Ratio of men to women (95% CI) | |
| **Drug group** | **2004** | **2017** | **2004** | **2017** |
| All drug poisoning deaths | 6.86 (6.01-7.72) | 8.08 (7.25-8.91) | 1.68 (1.65-1.72) | 2.38 (2.35,2.40) |
| Any CNS depressant drug | 5.61 (4.84-6.38) | 6.38 (5.65-7.11) | 1.62 (1.58-1.66) | 2.17 (2.14-2.19) |
| 2 or more CNS depressant drugs | 2.16 (1.69-2.63) | 3.56 (3.02-4.09) | 1.11 (1.01-1.20) | 2.35 (2.29-2.40) |
| Prescription opioids | 2.03 (1.61-2.46) | 3.01 (2.52-3.51) | 1.66 (1.56-1.76) | 1.93 (1.86-1.99) |
| Benzodiazepines | 1.59 (1.18-1.99) | 2.84 (2.36-3.32) | 0.81 (0.68-0.94) | 2.34 (2.28-2.41) |
| Antidepressants | 1.28 (0.90-1.67) | 1.47 (1.14-1.83) | 0.42 (0.22-0.62) | 1.06 (0.94-1.18) |
| Alcohol | 3.50 (2.87-4.14) | 2.79 (2.29-3.28) | 1.45 (1.38-1.52) | 2.30 (2.23-2.38) |

| | | | | |
|---|---|---|---|---|
| Cocaine | 0.37 (0.21-0.54) | 1.02 (0.75-1.30) | 8.36 (7.26-9.44) | 2.67 (2.49-2.86) |
| Heroin | 0.60 (0.37-0.82) | 1.51 (1.17-1.85) | 11.72 (10.64-12.80) | 6.00 (5.83-6.23) |

## Discussion

### *Summary of findings*

This repeated cross-sectional study found that there was a significant increase in overall drug poisoning deaths in Ireland during the period 2004 to 2017. The ASMR for drug poisoning deaths increased among men in the early years of the study, with no significant change in the latter stage of the study period. The ASMR for overall drug poisoning deaths among women remained stable.

A similar pattern was found among men when any CNS depressant drug was implicated in poisoning deaths, with a significant increase noted only for earlier years (2004 to 2008). In contrast, no significant increase was found for deaths among women involving any CNS depressant drug.

The increasing trend for two or more CNS depressant drugs implicated in drug poisoning deaths, especially the more recent significant increase among women, is of concern. This finding suggests that combinations of CNS depressant drugs may be impacting more on polydrug poisoning deaths in more recent years.

Our study findings differ from that reported in the U.S. where prescription opioids including fentanyl are the main drugs driving the increase in drug poisoning deaths.(2) In Ireland, while drug poisoning deaths involving prescription opioids have increased, deaths involving fentanyl remain very low.(15) Cocaine, antidepressants and benzodiazepines; especially when combined with other CNS depressant drugs, were observed to have the highest increasing trend in drug poisoning deaths in Ireland.

Our previous research has shown a stronger association of methadone being present as part of a combination of CNS depressant drugs in drug poisoning deaths among women

relative to men.(30) This current study found the majority of deaths involving prescription opioids related to methadone (both prescribed and illicit), similar to findings in the U.K.,(14) with women disproportionately affected. Compared to men, a higher percentage of women who died from a drug poisoning death involving methadone were registered for AOT at the time of their death, even though fewer women receive OAT in Ireland.(31) A growing body of evidence suggests that mortality risk during OAT is time varying.(32) As a full opioid agonist, methadone can cause hazardous respiratory depression and is associated with an elevated risk of drug poisoning during the first four weeks of treatment initiation.(32-35) The treatment timeframe for individuals included in this study is unknown. The risk of drug poisoning mortality immediately following OAT dropout, particularly the first four weeks is also high.(33-36) Given that clients' treatment status on the OAT register remains active for up to four weeks from their first day of non-attendance with their treatment provider, we cannot ascertain whether clients had dropped out of treatment. It is plausible that many clients who died of a drug poisoning death while registered on the OAT register had in fact left treatment because global evidence clearly demonstrates the protective effects of treatment versus leaving treatment.(37) Future work is necessary to ascertain whether the drugs involved in drug poisoning deaths vary depending on where a client is in terms of their OAT journey at the time of death.

It is imperative that there is increased awareness among prescribers and people who use drugs, of the differences between men and women in drug metabolism and drug action, as well as the risks associated with both prescribing and consuming multiple CNS depressant drugs. Benzodiazepines were the most common drug group in poisoning deaths involving two or more CNS depressant drugs, therefore the combination of benzodiazepines with other CNS depressant drugs warrants further investigation. Polydrug use has been recognised as an area of public health concern and has been described as "the norm" among people who use

drugs.(38) Polydrug use, especially opioids with sedative drugs, including benzodiazepines, have been associated with active post-traumatic stress disorder,(39) and with serious health risks including drug poisoning deaths.(40)

This study found that for women, drug poisoning deaths involving prescription opioids, benzodiazepines and/or antidepressants increased during the study period. This result contributes to a growing body of research highlighting opioids, benzodiazepines and antidepressants as the main drugs involved in drug poisoning deaths among women.(11)

The increased availability of illicit ('street') drugs especially benzodiazepines (including illicit alprazolam and diazepam) and illicit prescription opioids (such as methadone), certainly contribute to drug poisoning deaths. However, the main drugs involved in drug poisoning deaths are prescription drugs which are commonly prescribed, and it is not always recorded in data sources if these drugs were prescribed to the deceased individual. Therefore, increased monitoring of prescribing practices, in addition to enabling and enforcing use of electronic prescriptions, is required. Implementation of a national prescription monitoring system and linkage of NDRDI data to dispensed prescription data would assist in confirming whether drug(s) involved in drug poisoning deaths were prescribed to the individual or obtained illicitly at the time of death. A national prescription monitoring system would provide important insights into the supply, availability, and appropriate prescribing of prescription drugs with potential for misuse in Ireland.

Our study showed a significant association, for both sexes, (albeit marginal for women), between the rate of antidepressants dispensed and the rate of poisoning deaths involving antidepressants. While this does not indicate causality it does suggest a relationship. However, in observational studies of this sort, the possibility of residual confounding may remain a problem. Therefore associations identified in this study should be viewed principally as hypothesis generating and subject to further testing and verification in

future national cohort studies. Men are known to have higher rates of suicide, substance use disorder and neurodevelopment disorders relative to women.(41) Other mental health issues such as anxiety and depression are reported to be higher among women relative to men; however, this may be as a result of reporting bias among men who tend to mask their symptoms more than women.(41) Taking this into consideration, the higher rates of prescribing of antidepressants among men may be an indirect indicator of more men seeking medical help for mental health issues. This increase in prescribing correlates with results from a population prevalence study which showed an increasing trend in use of antidepressants among both men and women.(42) Further research is necessary into the type of antidepressants: both dispensed and implicated in drug poisoning deaths, as well as their impact on suicide deaths by drug poisoning.

Per capita consumption of alcohol has been shown to be an important determinant of alcohol-related deaths which include drug poisoning deaths.(43) Per capita consumption of alcohol in Ireland decreased during the study period.(44) Our results are in line with this as they show a decrease in drug poisoning deaths involving alcohol over the same period, with a significant decrease noted for women. This is a welcome finding and may indicate a relationship between decreased consumption and decreased alcohol poisoning deaths, thus emphasising the need for full implementation of the Public Health (Alcohol) Bill 2018,(45) in Ireland. Of note, as alcohol is a CNS depressant, and given the high presence of other CNS depressants in polydrug poisoning deaths involving alcohol, prescribers should assess for and advise on alcohol use when prescribing CNS depressant drugs.

Following an increase in the early years of the study period, rates of drug poisoning deaths involving cocaine decreased for men and women at a time of economic recession in Ireland.(46) Our findings show that as the economy improved post-recession, there was a significant increase in cocaine-related drug poisoning deaths for both sexes, similar to that

seen in other jurisdictions,(47) with the increase more substantial among women. Results from a national prevalence study during the study period also showed that while there was no significant increase in recent (last month) use of cocaine among men, there was a significant increase in recent use of cocaine among women.(42) In addition, in recent years there has been an increase in people seeking treatment related to cocaine use,(9) with an increase in the proportion of women in receipt of treatment for cocaine during the latter years of the study.(48) This trend highlights the impact of market forces on drug poisoning deaths and reflects the need to extend education and treatment related to cocaine use, especially for women.

### *Clinical and policy implications*

The increasing trend of CNS depressant drugs involved in drug poisoning deaths may indicate both increased use of these drugs to treat or cope with both addiction and other mental health issues, in addition to inappropriate (including illicit) use of these drugs by individuals in the community.

Increasing awareness in both the treatment settings and in the community, of the synergistic effect of taking multiple CNS depressant drugs, including alcohol, is warranted. This should include engagement with advocacy groups who work with people who use drugs, to promote the dissemination of harm reduction information to harder to reach groups, including those who are homeless. In addition, increased awareness among medical practitioners of the physiological sex differences affecting drug activity, when prescribing CNS depressant drugs is important. These differences include slower renal clearance of certain CNS depressant drugs, including pregabalin; women being more sensitive to and experience enhanced effectiveness of opioids; and benzodiazepines having a longer duration of action for women.(16, 17) Similar to that reported in other European countries,(49) Ireland does not have a national prescription drugs monitoring system. Such a system would

assist with pharmacovigilance and with identifying and monitoring trends in the misuse of prescription drugs.

The significant increase in deaths involving benzodiazepines in both men and women is of concern. The decreasing rate of benzodiazepines dispensed through the PCRS-GMS system appears to correspond with changes in policy, which introduced stricter prescribing regulations.(50) However, given the increase in illicit benzodiazepines in the community, as indicated by the increase in seizure data, and reports from experts in the area,(51) tighter controls on prescribing benzodiazepines may have partially resulted in an increased use of illicit benzodiazepines. These illicit benzodiazepines have higher potency and are available at low cost.(52) Due to the shorter half-life of illicit benzodiazepines, people who use these drugs tend to take repeated dosages which increases the risk of a poisoning death.

In Ireland, there were no national guidelines for benzodiazepine maintenance treatment. However, during the COVID-19 pandemic; benzodiazepine maintenance treatment was offered to homeless clients on OAT with established benzodiazepine dependency.(53) In 2019, 10% of clients in receipt of treatment for drug use in Ireland, reported benzodiazepines as their primary problem drug while 35% reported benzodiazepines as an additional problem drug.(48) While it is unknown what proportion of drug poisoning deaths since 2017 involved benzodiazepines, the United Nations Office on Drugs and Crime,(54) indicated in 2017 that polydrug use, particularly with benzodiazepines, may be linked to the increase in prescription opioid deaths. Misuse of benzodiazepines is a growing public health threat, with benzodiazepines identified as one of the most commonly misused prescription drugs.(55) Given the increasing risk of drug poisoning deaths involving benzodiazepines, continuation of and improved access to maintenance treatment, along with guidelines, and detoxification for people who are known to be misusing or dependent on benzodiazepines, should be considered. Research has shown that brief interventions

delivered in the primary care setting are effective in both reducing and discontinuing long term benzodiazepine use.(55)

While it is disappointing to see no significant decrease in deaths involving heroin, the stabilisation of rates for drug poisoning deaths involving heroin may be due to increased access to treatment, and/or it may reflect drug markets or drug use patterns among the population. Of note, prevalence data also indicate a stabilisation in the use of heroin in the population.(42) It is known that between 2010 and 2011 there was a severe shortage of heroin in the European market,(56) the reasons for which were multifaceted. In Ireland the heroin drought was reflected in a decrease in heroin poisoning deaths in 2011, but this decrease was counterbalanced by an increase in drug poisoning deaths involving benzodiazepines and methadone.(15) The heroin drought may be an example of how despite the lack of heroin, the underlying problem of drug addiction did not dissipate. Drug markets influence changing patterns in drug use so with a decrease in availability of heroin, people who used heroin may have had no alternative but to revert to using other drugs. This was observed in Australia, with an increase in cocaine and methamphetamine use during a period of reduced heroin availability.(57), (58)

Internationally there has been a decrease in recent years in the number of new treatment entries for OAT.(9, 48) However, data from 2018 shows a significant increase in heroin seizures in the European Union.(9) This, in combination with recent evidence from Australia showing an increase in deaths involving heroin,(59) indicates that heroin remains a main contributor to drug-related harm including drug poisoning deaths worldwide.

Although beyond the scope of this study, it would be of interest to assess the impact of the codeine dispensing guidelines for non-prescription products containing codeine (introduced in Ireland in 2010),(60) on drug poisoning deaths involving opioids.

In an effort to prevent drug poisoning deaths among both men and women, a combination of pharmacological, psychosocial and harm reduction interventions, with increasing access to sex-specific and age appropriate treatment and wider availability of naloxone, should be implemented.(61, 62) Promoting more open communication between prescribers and clients should enhance provision of appropriate treatment and help clients make informed decisions about their drug use. Innovative models of virtual healthcare delivery, such as those adapted during the COVID-19 pandemic, could also help minimise barriers to accessing services. Consideration should be given to incorporating this model of care, in addition to face to face consultations, in future delivery of treatment.(63) Services tailored to the particular needs of women are also required, such as increasing the number of residential treatment beds with childcare facilities.

Advocates for people who use drugs should be consulted on and contribute to policy decisions around harm reduction associated with drug use. Policies to reduce drug poisoning deaths should move from a criminal justice focus to a more public health focus.(64, 65) Harm reduction initiatives, along with treatment interventions, which include pharmaceutical combined with psychosocial assistance, need to focus on the range of problematic drugs. Furthermore, reducing stigma associated with drug use and drug poisoning deaths, aligned with actions to target economic deprivation, are required.

Future research in the area of drug poisoning deaths should include stratification by sex. Sex-specific evidence is required to support appropriate policy actions to reduce drug poisoning deaths.

## Strengths and limitations

The main strength of this study is the use of national data validated from a number of sources, ensuring accuracy and completeness of data available to examine trends in drug

poisoning deaths by sex. Access to prescription data for prescribed benzodiazepines and antidepressants enabled assessment of the relationship between trends in prescribing for and drug poisoning death rates involving these drugs.

The observation period of 2004 to 2017 is a strength of this study due to the many years of data included. Due to the nature of the death investigation and data collection processes, more recent data on drug poisoning deaths was not available. Future work will need to assess whether there have been any trend changes since 2017.

Limitations of this study include the reliance on individual Coroners to implicate drugs in poisoning deaths, which can be challenging when multiple drugs are present on a toxicology report. Information on whether the drugs were prescribed to the deceased is frequently not available in coronial files which limits the assessment of illicit use of these drugs and the impact of illicit drugs on these deaths.

Lack of data on private prescription drugs dispensed, limits analysis to those dispensed through the PCRS-GMS scheme, which covers approximately 40% of the general population. The PCRS-GMS scheme over-represents the more socially deprived and older aged populations, and therefore, does not represent the total population use of these drugs. In addition, the lack of data on consumption of other drugs (including prescription opioids, alcohol, cocaine, and heroin), stratified by sex, limited the analysis on these drugs.

Clients registered on the national opioid agonist treatment register can remain registered up to 30 days after leaving treatment. Therefore, data on clients in receipt of prescription opioids at the time of their death is incomplete. For this reason we were not able to assess the relationship between dispensing of prescription opioids and deaths involving prescription opioids.

## Conclusion

There is a need for an efficient healthcare response to polydrug use, which should include pragmatic harm reduction information around potentially lethal combinations of drugs, including alcohol, and how to reduce consumption of multiple drugs, especially CNS depressant drugs. Increased awareness of physiological sex differences affecting drug activity is required among both prescribers and people who use drugs. In addition to endorsement of a nationwide ePrescription system, an active national prescription monitoring system would assist in increased pharmacovigilance.

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## Author contributions

EL, KB, and GC contributed to the concept and design of the study. EL, KB, and SL each had a key role in acquisition of the data. EL undertook the statistical analysis with guidance from KB and GC. EL was responsible for the writing of the manuscript. KB, GC, and SL provided critical inputs to drafts of the paper. All authors contributed to the interpretation of the data, agree to be accountable for all aspects of the work, and approved the final manuscript.

## Declaration of Competing interest

No conflict declared.

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## Data Availability Statement

No additional data available.

## References


1. Shiels M S, Tatalovich Z, Chen Y, et al. Trends in Mortality From Drug poisonings, Suicide, and Alcohol-Induced Deaths in the United States From 2000 to 2017. *JAMA Netw Open,* 2020;**3**:e2016217. doi.org/10.1001/jamanetworkopen.2020.16217
2. Scholl L, Seth P, Kariisa M, et al. Drug and Opioid-Involved Overdose Deaths - United States, 2013-2017. *MMWR: Morb Mortal Wkly Rep,* 2019;67:1419-1427. doi.org/10.15585/mmwr.mm675152e1
3. Seth P, Scholl L, Rudd R. A, et al. Overdose Deaths Involving Opioids, Cocaine, and Psychostimulants - United States, 2015-2016. *Morb Mortal Wkly Rep,* 2018;**67**:349-358. doi.org/10.15585/mmwr.mm6712a1
4. McCall Jones C, Baldwi, G. T & Compton W M. Recent Increases in Cocaine-Related Overdose Deaths and the Role of Opioids. *American Journal of Public Health,* 2017;107:430-432. doi.org/10.2105/AJPH.2016.303627
5. Best A F, Haozous E A, Berrington de Gonzalez A, et al. Premature mortality projections in the USA through 2030: a modelling study. *Lancet Public Health,* 2018;3:e374-e384. doi.org/10.1016/S2468-2667(18)30114-2
6. Man N, Chrzanowska A, Dobbins T, et al. Trends in drug-induced deaths in Australia, 1997-2018. Drug Trends Bulletin Series. Sydney: National Drug and Alcohol Research Centre. 2019. https://ndarc.med.unsw.edu.au/resource/trends-drug-induced-deaths-australia-1997-2018 (accessed Sept 2020)
7. Kimber J, Hickman M, Strang J, et al. Rising opioid-related deaths in England and Scotland must be recognised as a public health crisis. *Lancet Psychiatry,* 2019;6:639-640. doi.org/10.1016/S2215-0366(19)30209-3

8. EMCDDA. European Drug Report 2014: Trends and Developments. 2014 https://www.emcdda.europa.eu/publications/edr/trends-developments/2014_en (assessed Oct 2020)

9. EMCDDA. European Drug Report 2020: Trends and Developments. 2020. https://www.emcdda.europa.eu/publications/edr/trends-developments/2020_en (assessed 25 Sept 2020)

10. Jalal H, Buchanich J M, Roberts M S et al. Changing dynamics of the drug overdose epidemic in the United States from 1979 through 2016. *Science,* 2018;361:6408. doi.org/10.1126/science.aau1184

11. Lynn E, Doyle A, Keane M, et al. Drug poisoning deaths among women: a scoping review. *J Stud Alcohol Drugs,* 2020;81:543-555. doi.org/10.15288/jsad.2020.81.543

12. Tweed E, Miller R, Mathesone C. Why are drug-related deaths among women increasing in Scotland? A scoping of possible explanations. Edinburgh: Scottish Government. 2018. http://www.gov.scot/publications/drug-related-deaths-women-increasing-scotland-9781787810129/(assessed Sept 2020)

13. Centers for Disease Control and Prevention. Prescription Painkiller Overdoses: A Growing Epidemic, Especially Among Women. 2013. https://www.cdc.gov/vitalsigns/prescriptionpainkilleroverdoses/index.html (assessed 7 March 2020)

14. Corkery JM, Schifano F, Ghodse AH, Oyefeso A. The effects of methadone and its role in fatalities. Hum Psychopharmacol. 2004; 19(8): 565-76. doi.org/10.1002/hup.630

15. Health Research Board. National Drug-Related Deaths Index 2008 to 2017 data. Health Research Board; 2019. https://www.drugsandalcohol.ie/31275 (assessed Oct 2020)

16. Algren D A, Monteilh C P, Punja M, et al. Fentanyl-associated fatalities among illicit drug users in Wayne County, Michigan (July 2005-May 2006). *Journal of Medical Toxicology,* 2013;9:106-115. doi.org/10.1007/s13181-012-0285-4

17. Whitley H, Lindsey W. Sex-based differences in drug activity. *Am Fam Physician,* 2009;80:1254-1258. doi.org/10.1016/S0140-6736(19)31812-4

18. VanHouten J P, Rudd R A, Ballesteros M F, et al. Drug Overdose Deaths Among Women Aged 30-64 Years - United States, 1999-2017. *MMWR: Morb Mortal Wkly Rep,* 2019;68:1-5. doi.org/10.15585/mmwr.mm6801a1

19. Osborn E. Deaths related to drug poisoning in England and Wales: 2017 registrations. Statistical bulletin. Office for National Statistics; 2018. https://www.ons.gov.uk/releases/deathsrelatedtodrugpoisoninginenglandandwales2017registrations (assessed Oct 2020).

20. Tyrrell E G, Orton E, Sayal K, et al. Differing patterns in intentional and unintentional poisonings among young people in England, 1998–2014: a population-based cohort study. *J Public Health (Oxf),* 2017;39:e1-e9. doi.org/10.1093/pubmed/fdw075

21. STROBE Statement. STROBE Statement. https://www.strobe-statement.org/fileadmin/Strobe/uploads/checklists/STROBE_checklist_v4_combined.pdf (assessed 30 May 2019)

22. Lynn E, Lyons S, Walsh S, et al. Trends in deaths among drug users in Ireland from traumatic and medical causes, 1998 to 2005. 2019 Dublin: Health Research Board. https://www.drugsandalcohol.ie/12775/ (assessed Sept 2020)

23. EMCDDA. Drug-Related Deaths (DRD) Standard Protocol, version 3.2. Lisbon: EMCDDA. 2010 https://www.emcdda.europa.eu/html.cfm/index107404EN.html_en (assessed Sept 2020)

24. Roxburgh A, Pilgrim J L, Hall W D, et al. Accurate identification of opioid overdose deaths using coronial data. *Forensic Sci Int,* 2018;287:40-46. doi.org/10.1016/j.forsciint.2018.03.032

25. Sinnott S J, Bennett K, Cahir C. Pharmacoepidemiology resources in Ireland-an introduction to pharmacy claims data. *Eur J Clin Pharmacol,* 2017;73:1449-1455. doi.org/10.1007/s00228-017-2310-7

26. Central Statistics Office. StatBank Annual Population Estimates. 2020. https://statbank.cso.ie/px/pxeirestat/Statire/SelectVarVal/Define.asp?maintable=PEA01&PLanguage=0 (assessed 15 Feb 2020)

27. Health Service Executive. Primary Care Reimbursement Service: Statistical Analysis of Claims and Payments 2008 to 2017. 2017. https://www.sspcrs.ie/portal/annual-reporting/report/annual (assessed 12 Sept 2020)

28. Eurostat. Revision of the European Standard Population – Report of Eurostat's Task Force. Luxembourg: European Commission. 2013. doi.org/10.2785/11470 (assessed Feb 2020)

29. National Cancer Institute. Joinpoint trend analysis softward. 2020 https://surveillance.cancer.gov/joinpoint/ (assessed 4 Aug 2020)

30. Lynn E, Cousins G, Lyons S, et al. A repeated cross-sectional study of factors associated with pregabalin-positive poisoning deaths in Ireland. *Drug Alcohol Depend,* 2020;206:107741. doi.org/10.1016/j.drugalcdep.2019.107741

31. Cousins G, Boland F, Barry J, et al. J-shaped relationship between supervised methadone consumption and retention in methadone maintenance treatment (MMT) in primary care: National cohort study. *Drug Alcohol Depend,* 2017;173: 126-131. doi.org/10.1016/j.drugalcdep.2016.12.009

32. Sordo L, Barrio G, Bravo M J, et al. Mortality risk during and after opioid substitution treatment: systematic review and meta-analysis of cohort studies. *Br Med J*, 2017;357: j1550. doi.org/10.1136/bmj.j1550

33. Cousins G, Teljeur C, Motterlini N, et al. Risk of drug-related mortality during periods of transition in methadone maintenance treatment: A cohort study. *J Subst Abuse Treat,* 2011;41:252-260. doi.org/10.1016/j.jsat.2011.05.001

34. Durand L, O'Driscoll D, Boland F, et al. Do interruptions to the continuity of methadone maintenance treatment in specialist addiction settings increase the risk of drug-related poisoning deaths? A retrospective cohort study. *Addiction*. 2020;115:1867-1877. doi.org/10.1111/add.15004

35. Evans E, Li L, Min J, et al. Mortality among individuals accessing pharmacological treatment for opioid dependence in California, 2006-10. *Addiction,* 2015;**110**:996-1005. doi.org/10.1111/add.12863

36. Kimber J, Larney S, Hickman M, et al. Mortality risk of opioid substitution therapy with methadone versus buprenorphine: a retrospective cohort study. *Lancet Psychiatry*, 2015;2:901-908. doi.org/10.1016/s2215-0366(15)00366-1

37. Santo T, Jr, Clark B, Hickman M, Grebely J, Campbell G, Sordo L, et al. Association of Opioid Agonist Treatment With All-Cause Mortality and Specific Causes of Death Among People With Opioid Dependence: A Systematic Review and Meta-analysis. JAMA Psychiatry. 2021. doi.org/10.1001/jamapsychiatry.2021.0976

38. Jarlenski M, Barry C L, Gollust S, et al. Polysubstance Use Among US Women of Reproductive Age Who Use Opioids for Nonmedical Reasons. *Am J Public Health,* 2017;107:1308-1310. doi.org/10.2105/AJPH.2017.303825

39. Hassan A, Le Foll B. Polydrug use disorders in individuals with opioid use disorder. *Drug Alcohol Depend,* 2019;198:28-33. doi.org/10.1016/j.drugalcdep.2019.01.031

40. Calcaterra S, Glanz J, Binswanger I. National trends in pharmaceutical opioid related overdose deaths compared to other substance related overdose deaths: 1999–2009. *Drug Alcohol Depend,* 2013;131:263-270. doi.org/10.1016/j.drugalcdep.2012.11.018

41. Affleck W, Carmichael V, Whitley R. Men's Mental Health: Social Determinants and Implications for Services. *Can J Psychiatry.* 2018;63:581-589. doi.org/10.1177/0706743718762388

42. National Advisory Committee on Drugs and Alcohol, Northern Ireland. Department of Health. Prevalence of drug use and gambling in Ireland & drug use in Northern Ireland. Bulletin 1. Dublin: National Advisory Committee on Drugs and Alcohol. 2016. https://www.drugsandalcohol.ie/26364/(assessed Oct 2020)

43. Norström T, Mäkelä,P. The connection between per capita alcohol consumption and alcohol-specific mortality accounting for unrecorded alcohol consumption: The case of Finland 1975–2015. *Drug Alcohol Rev*, 2019;38:731-736. doi.org/10.1111/dar.12983

44. Office of Revenue Commissioners. Excise Receipts by Commodity. 2020. https://www.revenue.ie/en/corporate/information-about-revenue/statistics/excise/receipts-volume-and-price/excise-receipts-commodity.aspx (assessed 4 July 2020)

45. Government of Ireland. Public Health (Alcohol) Act 2018. 2018. http://www.irishstatutebook.ie/eli/2018/act/24/enacted/en/html (assessed 14 Sept 2020)

46. Eurostat. General government deficit/surplus: % of GDP and million EUR. 2020.https://ec.europa.eu/eurostat/databrowser/view/tec00127/default/table?lang=en (assessed 23 Sept 2020)

47. Hedegaard H, Spencer M R, Garnett M F. Increase in drug overdose deaths involving cocaine: United States, 2009–2018. NCHS Data Brief No.384. Centre for Disease Control and Prevention. 2020. https://www.cdc.gov/nchs/data/databriefs/db384-H.pdf (assessed Oct 2020)

48. O'Neill D, Carew A, Lyons S. Drug Treatment in Ireland 2013 to 2019. Dublin: Health Research Board. 2020. https://www.drugsandalcohol.ie/32094 (assessed 19 Sept 2020)

49. Novak SP, Håkansson A, Martinez-Raga J, Reimer J, Krotki K, Varughese S. Nonmedical use of prescription drugs in the European Union. BMC Psychiatry. 2016;16(1):274. doi.org/10.1186/s12888-016-0909-3

50. Benzodiazepine Committee. Benzodiazepines: good practice guidelines for clinicians. Dublin: Department of Health and Children. 2002. https://www.drugsandalcohol.ie/5349/(assessed 27 Sept 2020)

51. Duffin T, Keane M, Millar S R. Street tablet use in Ireland. A Trendspotter study on use, markets, and harms. Dublin: Ana Liffey Drug Project. 2020. https://www.drugsandalcohol.ie/31872/(assessed Oct 2020)

52. Ryan V. 'Fake' benzos potency fears rise. *Irish Medical Times*. Dublin. 2020. https://www.imt.ie/news/fake-benzos-potency-fears-rise-31-08-2020/(assessed 31 Aug 2020)

53. O'Carroll A, Duffin T, Collins J. Harm reduction in the time of COVID-19: Case study of homelessness and drug use in Dublin, Ireland. *Int J Drug Policy,* 2021;87:102966. doi.org/10.1016/j.drugpo.2020.102966

54. UNODC. Global Smart Update Volume 18: Non-medical use of benzodiazepines: a growing threat to public health? ; 2017.

https://www.unodc.org/documents/scientific/Global_SMART_Update_2017_Vol_18.pdf (assessed 13 June 2021)

55. Lynch T, Ryan C, Hughes C M, et al. Brief interventions targeting long-term benzodiazepine and Z-drug use in primary care: a systematic review and meta-analysis. *Addiction,* 2020;115:1618-1639. doi.org/10.1111/add.14981

56. EMCDDA. Trendspotter Summary Report Recent Shocks in the European Heroin Market: Explanations and Ramifications In. Lisbon: EMCDDA. 2011. https://www.emcdda.europa.eu/scientific-studies/2011/trendspotters-report_en (assessed Oct 2020)

57. Roxburgh A, Degenhardt L, Breen C. Changes in patterns of drug use among injecting drug users following changes in the availability of heroin in New South Wales, Australia. Drug Alcohol Rev. 2004;23(3):287-94. doi:10.1080/09595230412331289446

58. Degenhardt L, Conroy E, Gilmour S, Collins L. THE EFFECT OF A REDUCTION IN HEROIN SUPPLY IN AUSTRALIA UPON DRUG DISTRIBUTION AND ACQUISITIVE CRIME. The British Journal of Criminology. 2005;45(1):2-24. doi:10.1093/bjc/azh096

59. Australian Institute of Health and Welfare. Alcohol, tobacco & other drugs in Australia. 2020. https://www.aihw.gov.au/reports/phe/221/alcohol-tobacco-other-drugs-australia/contents/drug-types/illicit-opioids-heroin (assessed 3 Sept 2020)

60. The Pharmaceutical Society of Ireland. Non-prescription medicinal products containing codeine: Guidance for pharmacists on safe supply to patients. Dublin: The Pharmaceutical Society of Ireland. 2010. www.drugsandalcohol.ie/13191 (assessed 6 Oct 2020)

61. Fairbairn N, Coffin P O, Walley A Y. Naloxone for heroin, prescription opioid, and illicitly made fentanyl overdoses: Challenges and innovations responding to a dynamic epidemic. *Int J Drug Policy,* 2017;46:172-179. doi.org/10.1016/j.drugpo.2017.06.005

62. Degenhardt L, Grebely J, Stone J, et al. Global patterns of opioid use and dependence: harms to populations, interventions, and future action. *Lancet,* 2019;394:1560-1579. doi.org/10.1016/S0140-6736(19)32229-9

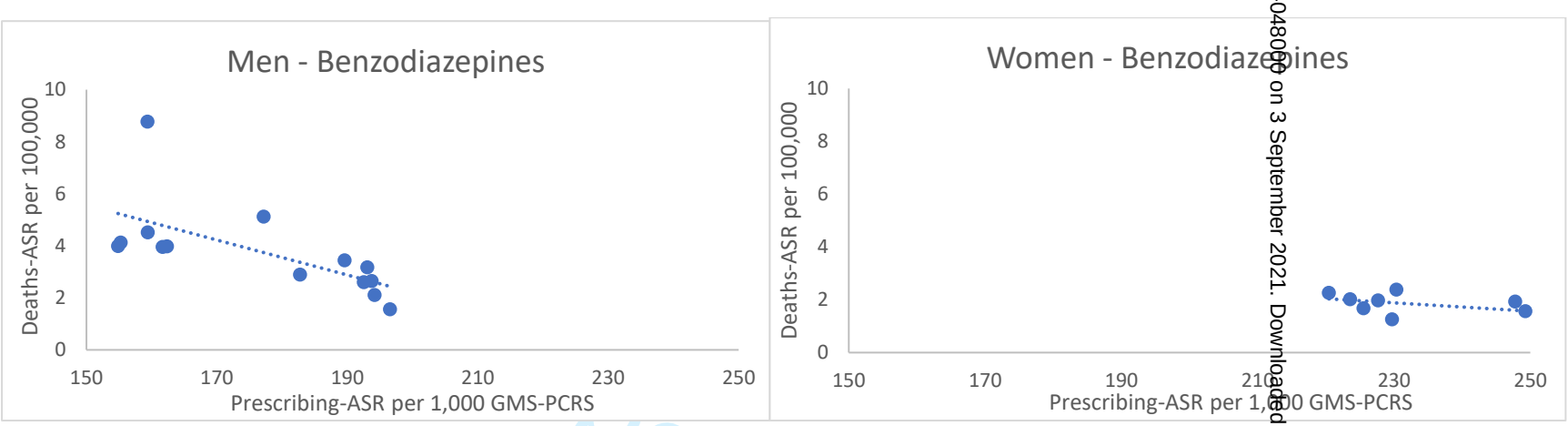
63. Crowley D, Delargy I. A national model of remote care for assessing and providing opioid agonist treatment during the COVID-19 pandemic: a report. *Harm Reduct J,* 2020;17:49. doi.org/10.1186/s12954-020-00394-z

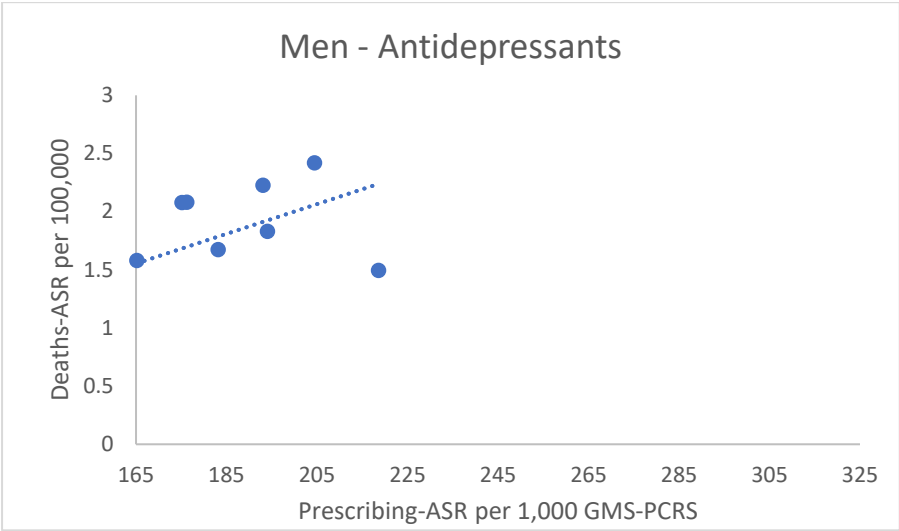
64. EMCDDA. Health and social responses to drug problems: a European guide. 2017. https://www.emcdda.europa.eu/publications/manuals/health-and-social-responses-to-drug-problems-a-european-guide_en (assessed 20 Sept 2020)

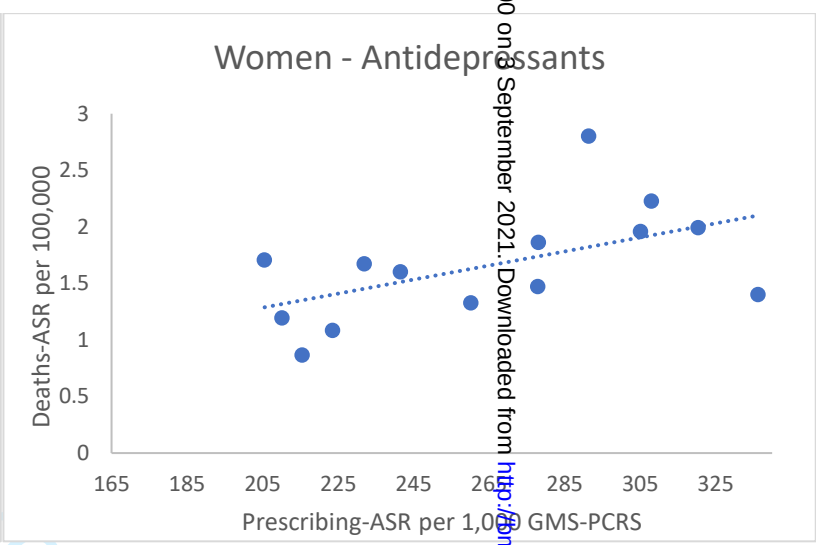
65. UNODC. Treatment and Care of people with Drug Use Disorders in Contact with the Criminal Justice System: Alternatives to Conviction or Punishment. 2016.https://www.unodc.org/unodc/en/drug-prevention-and-treatment/treatment-and-care-of-people-with-drug-use-disorders-in-contact-with-the-criminal-justice-system_-alternatives-to-conviction-or-punishment.html (assessed Oct 2020)

Figure 1. Benzodiazepines: Age-standardised rates per 100,000 of drug poisoning deaths involving benzodiazepines and age-standardised rates per 1,000 of individuals in receipt of prescribed benzodiazepines through the PCRS-GMR; 2004 to 2017.

Figure 2. Antidepressants: Age-standardised rates per 100,000 of drug poisoning deaths involving antidepressants and age-standardised rates per 1,000 of individuals in receipt of prescribed antidepressants through the PCRS-GMR; 2004 to 2017.





**Supplementary Table 1[Y]: Number of individual drug poisoning deaths, with breakdown of age group and drugs involved, by sex, NDRDI 2004 to 2017**

| | 2004 to 2008 n (%) | | | | 2009 to 2013 n (%) | | | | 2014 to 2017 n (%) | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Men | Women | Total | % of total | Men | Women | Total | % of total | Men | Women | Total | % of total |
| **All drug poisoning deaths** | 1145 (68.8) | 520 (31.2) | 1665 | | 1315 (71.3) | 529 (28.7) | 1844 | | 1022 (68.9) | 462 (31.1) | 1484 | |
| **Age Groups** | | | | | | | | | | | | |
| 13 to 24 years of age | 208 (80.9) | 49 (19.1) | 257 | 15.4 | 155 (81.2) | 36 (18.8) | 191 | 10.4 | 77 (80.2) | 19 (19.8) | 96 | 6.5 |
| 25 to 34 years of age | 351 (77.8) | 100 (22.2) | 451 | 27.1 | 403 (79.8) | 102 (20.2) | 505 | 27.4 | 239 (74.9) | 80 (25.1) | 319 | 21.5 |
| 35 to 44 years of age | 264 (70.8 | 109 (29.2) | 373 | 22.4 | 336 (76.9) | 101 (23.1) | 437 | 23.7 | 335 (72.0) | 130 (28.0) | 465 | 31.3 |
| 45 to 54 years of age | 192 (60.4) | 126 (39.6) | 318 | 19.1 | 232 (63.7) | 132 (36.3) | 364 | 19.7 | 209 (70.6) | 87 (29.4) | 296 | 19.9 |
| 55 or more years of age | 130 (48.9) | 136 (51.1) | 266 | 16.0 | 189 (54.5) | 158 (45.5) | 347 | 18.8 | 162 (52.6) | 146 (47.4) | 308 | 20.8 |
| | | | | | | | | | | | | |
| **Polydrugs (≥2 drugs) involved in the death** | | | | | | | | | | | | |
| Yes | 511 (66.5) | 257 (33.5) | 768 | 46.1 | 720 (70.0) | 309 (30.0) | 1029 | 55.8 | 614 (66.7) | 306 (33.3) | 920 | 62.0 |
| No | 634 (70.7) | 263 (29.3) | 897 | 53.9 | 595 (73.0) | 220 (27.0) | 815 | 44.2 | 408 (72.3) | 156 (27.7) | 564 | 38.0 |
| | | | | | | | | | | | | |
| **CNS depressant drugs involved in the death** | | | | | | | | | | | | |
| Yes | 915 (69.1) | 409 (30.9) | 1324 | 79.5 | 1122 (72.6) | 424 (27.4) | 1546 | 83.8 | 847 (68.8) | 384 (31.2) | 1231 | 83.0 |
| No | 230 (67.4) | 111 (32.6) | 341 | 20.5 | 193 (64.8) | 105 (35.3) | 298 | 16.2 | 175 (69.2) | 78 (30.8) | 253 | 17.0 |
| *Breakdown of CNS depressants drugs* | | | | | | | | | | | | |
| *Opioids (prescription (63%), heroin (37%))* | 627 (75.0) | 209 (25.0) | 836 | 63.1 | 841 (77.0) | 251 (23.0) | 1092 | 70.6 | 667 (71.3) | 268 (28.7) | 935 | 76.0 |
| *Alcohol* | 451 (65.9) | 233 (34.1) | 684 | 51.7 | 512 (72.3) | 196 (27.7) | 708 | 45.8 | 351 (70.6) | 146 (29.4) | 497 | 40.4 |
| *Benzodiazepines* | 275 (65.5) | 145 (34.5) | 420 | 31.7 | 490 (72.3) | 188 (27.7) | 678 | 43.9 | 409 (68.2) | 191 (31.8) | 600 | 48.7 |
| *Z-Drugs* | 28 (56.0) | 22 (44.0) | 50 | 3.8 | 102 (65.4) | 54 (34.6) | 156 | 10.1 | 160 (57.6) | 118 (42.4) | 278 | 22.6 |
| *Pregabalin* | 0 | 0 | 0 | | 9 (40.9) | 13 (59.1) | 22 | 7.4 | 97 (52.2) | 89 (47.8) | 186 | 73.5 |
| | | | | | | | | | | | | |
| **2 or more CNS depressant drugs involved** | | | | | | | | | | | | |
| Yes | 379 (68.3) | 176 (31.7) | 555 | 33.3 | 595 (73.5) | 215 (26.5) | 810 | 43.9 | 517 (67.4) | 250 (32.6) | 767 | 51.7 |
| No | 766 (69.0) | 344 (31.0) | 1110 | 66.7 | 720 (69.6) | 314 (30.4) | 1034 | 56.1 | 505 (70.4) | 212 (29.6) | 717 | 48.3 |
| *Breakdown of ≥2 CNS depressants drugs* | | | | | | | | | | | | |
| *Opioids (prescription (63%), heroin (37%))* | 365 (74.8) | 123 (25.2) | 488 | 87.9 | 616 (78.2) | 172 (21.8) | 788 | 97.3 | 539 (71.1) | 219 (28.9) | 758 | 98.8 |
| *Benzodiazepines* | 261 (66.6) | 131 (33.4) | 392 | 70.6 | 473 (73.3) | 172 (26.7) | 645 | 79.6 | 398 (68.6) | 182 (31.4) | 580 | 75.6 |
| *Alcohol* | 193 (64.8) | 105 (35.2) | 298 | 53.7 | 236 (73.5) | 85 (26.5) | 321 | 39.6 | 174 (68.8) | 79 (31.2) | 253 | 33.0 |
| *Z-Drugs* | 26 (60.5) | 17 (39.5) | 43 | 7.7 | 89 (63.6) | 51 (36.4) | 140 | 17.3 | 147 (56.8) | 112 (43.2) | 259 | 33.8 |
| *Pregabalin* | 0 | 0 | 0 | | 8 (38.1) | 13 (61.9) | 21 | 2.0 | 90 (51.1) | 86 (48.9) | 176 | 24.5 |
| | | | | | | | | | | | | |
| **Rx Opioids** | 346 (66.5) | 174 (33.5) | 520 | 31.2 | 481 (69.7) | 209 (30.3) | 690 | 37.4 | 384 (63.7) | 219 (36.3) | 603 | 40.6 |
| Most commonly | | | | | | | | | | | | |
| Methadone | 206 (73.6) | 74 (26.4) | 280 | 53.8 | 332 (77.8) | 95 (22.2) | 427 | 61.9 | 270 (68.4) | 125 (31.6) | 395 | 65.5 |
| Codeine | 28 (47.5) | 31 (52.5) | 59 | 11.3 | 58 (54.7) | 48 (45.3) | 106 | 15.4 | 33 (44.0) | 42 (56.0) | 75 | 12.4 |
| Tramadol | 19 (42.2 | 26 (57.8) | 45 | 8.7 | 54 (53.5) | 47 (46.5) | 101 | 14.6 | 49 (54.4) | 41 (45.6) | 90 | 14.9 |
| Fentanyl* | ~ | 0 | ~ | | ~ | ~ | 6 | 0.9 | 15 (60.0) | 10 (40.0) | 25 | 4.1 |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Polydrug deaths (67.5% involved benzodiazepines) | 243 (65.5) | 128 (34.5) | 371 | 71.3 | 410 (70.7) | 170 (29.3) | 580 | 84.1 | 336 (63.2) | 196 (36.8) | 532 | 88.2 |
| **Benzodiazepines** | 275 (65.5) | 145 (34.5) | 420 | 25.2 | 490 (72.3) | 188 (27.7) | 678 | 36.8 | 409 (68.2) | 191 (31.8) | 600 | 40.4 |
| Most commonly | | | | | | | | | | | | |
| Diazepam | 177 (67.3) | 86 (32.7) | 263 | 62.6 | 375 (77.0) | 112 (23.0) | 487 | 71.8 | 300 (71.9) | 117 (28.1) | 417 | 69.5 |
| Flurazepam | 57(60.0) | 38 (40.0) | 95 | 22.6 | 112 (64.7) | 61 (35.3) | 173 | 25.5 | 96 (64.9) | 52 (35.1) | 148 | 24.7 |
| Alprazolam | 9 (90.0) | 1 | 10 | 2.4 | 76 (69.7) | 33 (30.3) | 109 | 16.1 | 137 (67.2) | 67 (32.8) | 204 | 34.0 |
| Polydrug deaths (60% involved Rx Opioids) | 268 (65.4) | 142 (34.6) | 410 | 97.6 | 485 (73.6) | 174 (26.4) | 659 | 97.2 | 405 (68.2) | 189 (31.8) | 594 | 99.0 |
| **Antidepressants** | 129 (51.0) | 124 (49.0) | 253 | 15.2 | 190 (49.4) | 195 (50.6) | 385 | 20.9 | 181 (51.0) | 174 (49.0) | 355 | 23.9 |
| Most commonly | | | | | | | | | | | | |
| Citalopram | 30 (44.1) | 38 (55.9) | 68 | 26.9 | 61 (55.0) | 50 (45.0) | 111 | 28.8 | 38 (51.4) | 36 (48.6) | 74 | 20.8 |
| Amitriptyline | 31 (55.4) | 25 (44.6) | 56 | 22.1 | 28 (37.3) | 47 (62.7) | 75 | 19.5 | 43 (52.4) | 39 (47.6) | 82 | 23.1 |
| Venlafaxine | 17 (63.0) | 10 (37.0) | 27 | 10.7 | 22 (44.9) | 27 (55.1) | 49 | 12.7 | 16 (40.0) | 24 (60.0) | 40 | 11.3 |
| Polydrug deaths (61% involved benzodiazepines) | 106 (50.2) | 105 (49.8) | 211 | 83.4 | 174 (51.8) | 162 (48.2) | 336 | 87.3 | 164 (51.4) | 155 (48.6) | 319 | 89.9 |
| **Alcohol** | 451 (65.9) | 233 (34.1) | 684 | 41.1 | 512 (72.3) | 196 (27.7) | 708 | 38.4 | 351 (70.6) | 146 (29.4) | 497 | 33.5 |
| Polydrug deaths (30% involved benzodiazepines) | 225 (64.7) | 123 (35.3) | 348 | 50.9 | 265 (71.8) | 104 (28.2) | 369 | 52.1 | 195 (69.6) | 85 (30.4) | 280 | 56.3 |
| **Cocaine** | 195 (83.0) | 40 (17.0) | 235 | 14.1 | 131 (84.0) | 25 (16.0) | 156 | 8.5 | 142 (77.6) | 41 (22.4) | 183 | 12.3 |
| Polydrug deaths (54% involved benzodiazepines) | 126 (82.4) | 27 (17.6) | 153 | 65.1 | 119 (83.8) | 23 (16.2) | 142 | 91.0 | 125 (76.7) | 38 (23.3) | 163 | 89.1 |
| **Heroin** | 281 (88.9) | 35 (11.1) | 316 | 19.0 | 360 (89.6) | 42 (10.4) | 402 | 21.8 | 283 (85.2) | 49 (14.8) | 332 | 22.4 |
| Polydrug deaths (65% involved benzodiazepines) | 178 (87.3) | 26 (12.7) | 204 | 64.6 | 241 (87.3) | 35 (12.7) | 276 | 68.7 | 232 (85.6) | 39 (14.4) | 271 | 81.6 |

~ = value less than 5

* Although fentanyl is not one of the main prescription opioid drugs involved in drug poisoning deaths in Ireland, data displayed for information purposes

ˠ This is a multi-response analysis taking into account up to six drugs implicated in any one death, therefore individual rows will not equal totals.

**STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional studies***

| Section/Topic | Item # | Recommendation | Reported on page # |
|---|---|---|---|
| **Title and abstract** | 1 | (*a*) Indicate the study's design with a commonly used term in the title or the abstract | 1 |
| | | (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found | 2 |
| **Introduction** | | | |
| Background/rationale | 2 | Explain the scientific background and rationale for the investigation being reported | 4 |
| Objectives | 3 | State specific objectives, including any prespecified hypotheses | 5 |
| **Methods** | | | |
| Study design | 4 | Present key elements of study design early in the paper | 5-6 |
| Setting | 5 | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection | 6 |
| Participants | 6 | (*a*) Give the eligibility criteria, and the sources and methods of selection of participants | 6-10 |
| Variables | 7 | Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable | 8 |
| Data sources/ measurement | 8* | For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group | 6-10 |
| Bias | 9 | Describe any efforts to address potential sources of bias | |
| Study size | 10 | Explain how the study size was arrived at | |
| Quantitative variables | 11 | Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why | 6-10 |
| Statistical methods | 12 | (*a*) Describe all statistical methods, including those used to control for confounding | 8-10 |
| | | (*b*) Describe any methods used to examine subgroups and interactions | 9-10 |
| | | (*c*) Explain how missing data were addressed | |
| | | (*d*) If applicable, describe analytical methods taking account of sampling strategy | |
| | | (*e*) Describe any sensitivity analyses | |
| **Results** | | | 10 |

| | | | |
|---|---|---|---|
| Participants | 13* | (a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed | 10 |
| | | (b) Give reasons for non-participation at each stage | |
| | | (c) Consider use of a flow diagram | |
| Descriptive data | 14* | (a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders | 10-15 |
| | | (b) Indicate number of participants with missing data for each variable of interest | |
| Outcome data | 15* | Report numbers of outcome events or summary measures | 10-15 |
| Main results | 16 | (*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included | 10-16 |
| | | (*b*) Report category boundaries when continuous variables were categorized | |
| | | (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period | |
| Other analyses | 17 | Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses | 10-16 |
| **Discussion** | | | |
| Key results | 18 | Summarise key results with reference to study objectives | 16-20 |
| Limitations | 19 | Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias | 24-25 |
| Interpretation | 20 | Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence | 16-25 |
| Generalisability | 21 | Discuss the generalisability (external validity) of the study results | 16-23 |
| **Other information** | | | |
| Funding | 22 | Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based | 26 |

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.