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Research Paper

A national case fatality study of drugs taken in intentional overdose

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ABSTRACT

Background: Intentional drug overdose (IDO) has been linked with marked increases in premature mortality risk due to suicide, accidents and other causes, yet little is known about how case fatality risk varies according to the type of drug/s taken. This study aimed to examine the incidence of IDO, to identify the predictors of fatal IDO and to establish which drugs are linked with greater risk of a fatal outcome.

Methods: Data from the National Self-Harm Registry, and the National Drug-Related Deaths Index, 2007–2014, were used to calculate incidence, examine overdose characteristics and estimate case fatality risk ratios.

Results: We examined 63,831 non-fatal and 364 fatal IDOs (incidence: 148.8 and 1.01 per 100,000 respectively). Compared to non-fatal IDOs, fatal cases were more often male (55.2% vs. 42.0%), older in age (median 44 vs. 35 years), and more frequently involved multiple drugs (78.3% vs. 48.5%). Tricyclic antidepressants were associated with a 15-fold increased risk of death and opioids a 12-fold increased risk, relative to the reference category (non-opioid analgesics). While the risk of fatal outcome was higher for males than females, the elevation in risk was greater in females when tricyclic antidepressants or opioids were taken.

Conclusion: Male gender, increasing age and multiple drug use were associated with fatal IDO outcome. Tricyclic antidepressants and opioids were associated with a significantly increased risk of death following intentional overdose. Clinicians need to consider the case fatality risk of drugs when determining treatment for patients at risk of or those who have previously harmed themselves.

Introduction

Intentional drug overdose (IDO) is the most common method of hospital-presenting non-fatal self-harm (Perry et al., 2012; Vancayseele, Portzky & van Heeringen, 2016), and is associated with an increased risk of repeat self-harm (Finkelstein et al., 2016). The risk of mortality due to suicide is also increased among persons who have engaged in IDO, as are deaths due to other causes, including accidents and natural deaths caused by illness (Finkelstein et al., 2015a, ; 2015b).

Intentional drug overdose resulted in 7792 presentations to Irish hospitals in 2018 (Griffin et al., 2019), and accounts for approximately 68–84% of all hospital-treated self-harm presentations, most of which involve females and persons under 40 years of age (Daly et al., 2018; Vancayseele, Rotsaert, Portzky & van Heeringen, 2019). Fatal IDO results in approximately 40 deaths in Ireland annually (CSO, 2014), and accounted for approximately 889 deaths in England and Wales in 2018 (ONS, 2019), of which the majority are among males. Considering drugs taken, non-fatal IDOs most frequently involve non-opioid analgesics, antidepressants and hypnotic sedatives (including benzodiazepines) (Daly et al., 2018; Vancayseele et al., 2019), and fatal IDOs most commonly involve opioids and benzodiazepines (HRB, 2015; Pringle et al., 2017).

The type of drug taken in IDO varies according to individual characteristics, geography and across time periods, and is one of several key

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factors that influence the likelihood of repeat IDO and subsequent fatality following overdose (Finkelstein et al., 2016; Geulayov et al., 2018). Research in England and Wales, which measured case fatality of single-drug overdoses with antidepressants and benzodiazepines attributed high fatality to the antidepressants dosulepin, doxepin, citalopram (Hawton et al., 2010), and to the benzodiazepine and hypnotic drugs temazepam and zopiclone/zolpidem (Geulayov et al., 2018). A subsequent study in the USA examined the fatality of drugs used in all poisoning deaths (intentional and accidental) over a 16-year period, and identified opioids as the most toxic drug examined, followed by tricyclic antidepressants (Brett, Wylie, Raubenheimer, Isbister & Buckley, 2019).

Establishing the potential fatality of an IDO is undermined by the frequent involvement of a combination of multiple drugs in overdose. Multiple drugs are present in between 26 and 41% of non-fatal IDOs (Daly et al., 2018; Finkelstein et al., 2016), increasing to 64% in fatal overdoses (HRB, 2015). Despite the involvement of multiple drugs in IDO, the case fatality of drugs taken in multiple drug IDO remains under-researched and has not yet been established in relation to suicide deaths. Insights into the case fatality of drugs used in both single and multiple drug IDOs would aid clinicians in determining the appropriate treatment pathways for patients who are at increased risk of or have previously engaged in IDO.

This study aimed to estimate the incidence of fatal and non-fatal IDO, to identify the predictors of fatal IDO, and to establish which drug types are most strongly linked with a fatal outcome, according to case fatality risk estimates.

Method

This was an observational study using data pertaining to the period 1st Jan 2007 to 31st Dec 2014, which examined two unlinked datasets that captured fatal IDO cases in the National Drug-Related Deaths Index, Ireland (NDRDI) and non-fatal IDO presentations in the National Self-Harm Registry Ireland (NSHRI).

Non-fatal hospital-treated IDO presentations

The NSHRI, which is administered by the National Suicide Research Foundation (NSRF), monitors hospital-treated self-harm across all 36 acute hospitals in the Republic of Ireland, using the following definition of self-harm: 'an act with non-fatal outcome in which an individual deliberately initiates a non-habitual behavior, that without intervention from others will cause self-harm, or deliberately ingests a substance in excess of the prescribed or generally recognised therapeutic dosage, and which is aimed at realizing changes that the person desires via the actual or expected physical consequences' (Platt et al., 1992). Data on self-harm presentations are collected by independently trained Data Registration Officers (DROs), including items detailing: sex, age, area of residence, date and hour of hospital attendance, whether the individual arrived by ambulance, method(s) of self-harm, drugs taken, medical card status, mental health assessment and recommended next care received. A maximum of five methods are recorded for presentations involving multiple methods. We examined non-fatal IDO presentation-based data, identified as having International Statistical Classification of Diseases and Related Health Problems, 10th revision codes (ICD-10) X60-X64. Presentations of IDO involving other agents, such as chemicals (ICD-10 X60-X69), and alcohol-only self-poisoning cases (ICD-10 X65) were excluded. Drugs taken in non-fatal IDO are captured via hospital medical records including casualty card notes, clinical notes, ambulance records, mental health assessment notes and toxicology reports if available. Information pertaining to self0harm methods, drugs used and quantities consumed are self-reported by the patient. A maximum of 10 drugs per IDO episode were included.

Fatal IDO cases

Deaths by IDO were obtained via the NDRDI, which records all deaths by drug and/or alcohol poisoning, and deaths among drug users and those who are alcohol dependent, in persons aged over 15 years in the Republic of Ireland. Fatal cases where the Coroner returned a suicide or 'open' verdict (i.e. unnatural death of undetermined cause), following a completed inquest procedure, were included in this study. Open verdicts are customarily included in suicide statistics as these cases have been shown to have similar characteristics to suicides, often representing probable suicides where the evidence was insufficient to prove that the individual intended to take their own life (Linsley, Schapira & Kelly, 2001). Fatal IDO cases are those that occurred directly due to the toxic effects of the drug(s) taken. Non-poisoning deaths, deaths by alcohol only (ICD-10 X65), chemical poisonings (ICD-10 X66-X69), and deaths with no coronial verdict, or with a verdict of misadventure, were excluded. Relevant information collected on each fatal IDO case included: sex, age date of death and postmortem toxicology results - including whether a drug was involved in death or caused the death, as reported on the individual's death certificate.

Drugs certified as a cause of death or involved in death

Postmortem blood and urine samples are screened in local hospital laboratories using immunoassay analysis to identify the involvement of particular drugs in death. Further identification and quantification, is provided by the State Laboratory for Human Toxicology which, together with information from the State Pathologist, assists the responsible Coroner in interpreting the role of each drug taken in fatal IDO, which is classified as either involved in or causal to death. One or more drugs can be registered on the individuals' certificate as being involved in death or as having caused death.

Classification of drugs

We reported on the drug types frequently used in IDO, as determined in a previous study (Daly et al., 2018). The Anatomical Therapeutic Chemical (ATC) classification system was applied to the drugs examined in this study, the detail of which can be found in the Guidelines for ATC Classification and DDD Assignment (WHO, 2019). The ATC codes for the drug types reported are: psycholeptics 'N05'; analgesics 'N02'; opioids 'N02A'; morphine containing drugs 'N02AA01', 'N02AG01', 'N02AA51'; oxycodone containing drugs 'N02AA05', 'N02AJ17', 'N02AJ18', 'N02AJ19'; tramadol containing drugs 'N02AX02', 'N02AJ13', 'N02AJ14', 'N02AJ15'; non-opioid analgesics 'N02B' and 'N02C'; hypnotics and sedatives 'N05C'; antipsychotics; 'N05A'; psychoanaleptics 'N06'; selective serotonin reuptake inhibitors (SSRIs) 'N06AB'; fluoxetine 'N06AB03'; citalopram 'N06AB04'; sertraline 'N06AB06'; tricyclic antidepressants 'N06AA'; amitriptyline 'N06AA09'; dosulepin 'N06AA16'; trimipramne 'N06AA06'; antiepileptics 'N03'; benzodiazepines 'N03AE', 'N05BA', 'N05CD' and 'N05CF'. Illicit drugs were identified using the Irish Misuse of Drugs Acts of 1977 and 1984 (Misuse of Drugs Act 1977; Misuse of Drugs Act 1984); and are listed in the Supplementary Material, item 'Illicit Drugs List'. Multiple drug use refers to the involvement of two or more distinct drug types per IDO presentation, whereas single drug use refers to the taking of just one drug type, both of which excluded alcohol involvement.

Statistical analyses and reporting

Annual gender- and age-specific incidence rates per 100,000 persons, including only persons aged 15 and over, were calculated using the numbers of non-fatal and fatal IDO cases recorded and the national Census population data for 2011 and the Central Statistics Office annual population estimates for other years. We calculated 95% confidence

intervals using the Poisson distribution. Case fatality risk represent the proportion of IDOs that are fatal according to the demographic or drug group under examination. Case fatality risk ratios represent the ratio of the case fatality risk of the particular demographic or drug group being examined relative to the reference category. Non-opioid analgesics were chosen as the reference category for drugs examined in Table 2 as they are among the most frequently used drugs taken in IDO (Daly et al., 2018). The reference categories for Table 3 are amitriptyline (tricyclic antidepressant), fluoxetine (SSRI antidepressant) and tramadol (opioid), which are the three specific drugs most commonly taken in IDO within their respective drug type category. Case fatality risk ratios of drugs presented within the main text of the paper refer to drugs that were certified within the individual's death certificate as being the cause of death, and were calculated from an age- and gender-adjusted Poisson regression model. An additional sensitivity analysis was conducted to estimate the case fatality risk ratios of drugs involved in death (see Supplementary Tables 2, 5 and 6).

A process of weighting was performed to address the challenge of calculating case fatality risk and case fatality risk ratios when multiple drugs had been certified as causing death. Case fatality risk ratios presented within this paper are weighted, whereby the drug of interest is counted as half within the reference drug group and half within the drug group of interest, in which the two aforementioned drug groups were attributed 50% of the fatality risk. A series of sensitivity analyses were conducted to calculate alternative case fatality risk ratio estimates whereby the drug of interest was either counted in both its drug group or that of the reference group ('Double count') or in neither ('Excluded in count'). These additional sensitivity analyses, which are provided in the Supplementary Material (Table 2, 4 and 5), offer alternative analytical approaches for estimating the relative fatality of IDOs according to the type of drug/s taken.

Cell counts of less than five for fatal cases were masked in all tabulations. Analyses were conducted using SPSS v.22. Statistical significance was reported at three thresholds: $p \leq 0.05$, $p \leq 0.01$ and $p \leq 0.001$. The conventional levels of $p \leq 0.05$, $p \leq 0.01$ are reported to allow for comparability with other research. The stringent threshold of $p \leq 0.001$ was used to highlight the most significant associations, which is important when examining a dataset of this size. Case fatality risk ratio weighting was performed using Excel formulae, and Stata IC 12 was subsequently employed to calculate the case fatality risk ratios and accompanying confidence intervals and significance values.

The reporting of this study conforms to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies.

Ethical approval

The NSHRI has ethical approval from the National Research Ethics Committee of the Faculty of Public Health Medicine, Ireland. The NSHRI operates under a policy approving a waiver of consent. These patients have the right to opt out of having their data collected and used for research via a system that is described in patient leaflets placed in emergency departments, and reserve all the rights of data subjects as outlined in the current General Data Protection Regulation (GDPR) 2018 regulations. The NDRDI has ethical approval from the Health Research Board (HRB) ethics committee.

Data access

The NSRF is registered with the Data Protection Agency and complies with the Irish Data Protection Act of 1988 and the Irish Data Protection (Amendment) Act of 2003. All data were anonymised and stored on a secure server in a restricted access location and accessed only via an encrypted computer.

Results

Characteristics of non-fatal and fatal IDOs

Between 1st January 2007 and 31st December 2014 there were 64,195 IDOs, 63,831 of which were non-fatal, and 364 of which were fatal. Of the fatal IDO cases, 46.2% ($n = 168$) had received a verdict of suicide and 53.8% ($n = 196$) an open verdict. The majority of fatal cases were male (55.2%) and the median age of these persons was 44 years (IQR: 33–53). Non-fatal IDO presentations were most often made by females (58.0%) and the median age reported was 35 years (IQR: 23–44). Multiple drug use was a factor in 78.3% of fatal IDOs and 48.5% of non-fatal IDOs.

Incidence of non-fatal and fatal IDOs

Figs. 1a and 1b illustrate the non-fatal and fatal IDO incidence rates stratified by age and gender. Overall, the rate of non-fatal IDO was 148.8 per 100,000 (95% CI 147.5–150.1) and the rate of fatal IDO was 1.01 (0.90–1.11). The incidence of non-fatal IDO was higher for females and peaked for persons aged 15–24 years whereas the rate of fatal IDO was higher for males and highest among persons aged 45–54 years, as illustrated in Figs. 1a and 1b and reported in Supplementary Table 1.

Case fatality by gender, age and number of drugs

Examining case fatality, the risk of death following an IDO was 1.7 times greater for males, compared to females (CFRR = 1.70; 1.38–2.09, $p \leq 0.001$), as reported in Table 1. The risk of death increased with age and was over five times greater for those aged 45 years or older (CFRR = 5.63; 3.91–8.11, $p \leq 0.001$), compared to those aged 15–24 years. Multiple drug IDOs were over three times more likely to be fatal compared to single drug IDOs (CFRR = 3.80; 2.96–4.88, $p \leq 0.001$). Intentional drug overdoses involving between two and five different drugs were three times more likely to be fatal (CFRR = 3.13; 2.43–4.04, $p \leq 0.001$) and those that involved six or more distinct drugs ($n = 365$) were also significantly more likely to result in death (CFRR = 60.5; 42.7–85.7, $p \leq 0.001$), compared to IDOs involving one drug. The absence of alcohol did not lessen the risk of death in this study (CFRR = 1.07; 0.87–1.32, $p = 0.538$).

Drugs frequently taken in IDO

Psycholeptic drugs, the majority of which were benzodiazepines, were the drug type that most frequently caused death or were involved in fatal and non-fatal IDO, as reported in Table 2. Considering non-fatal IDOs, non-opioid analgesics were frequently taken, with an incidence rate of 50.0 per 100,000 (49.3–50.8). Opioid and tricyclic antidepressant drugs had the lowest rates of involvement in non-fatal IDO at 7.85 (7.56–8.15) and 3.63 per 100,000 (3.43–3.83), respectively. Examining fatal IDOs, the frequent use of psycholeptic drugs was followed by antidepressant drugs at 0.39 (0.33–0.46). Owing to the larger number of female non-fatal IDO presentations, compared to males, the rates for all drugs used in non-fatal acts (excluding illicit drugs) are higher for females. Greater gender disparities are reported for fatal IDOs, where females have higher rates of IDOs involving antipsychotic and antidepressant drugs, as illustrated in Table 2. The incidence patterns were similar for drugs that were involved in death, as reported in Supplementary Table 2.

Case fatality of drugs which caused death

Table 2 reports on the case fatality of drugs that were deemed ultimately by the Coroners to have caused death. The risk of death following IDO was 15 times greater when a tricyclic antidepressant was taken (CFRR = 15.1; 9.90–23.2, $p \leq 0.001$), compared to the reference

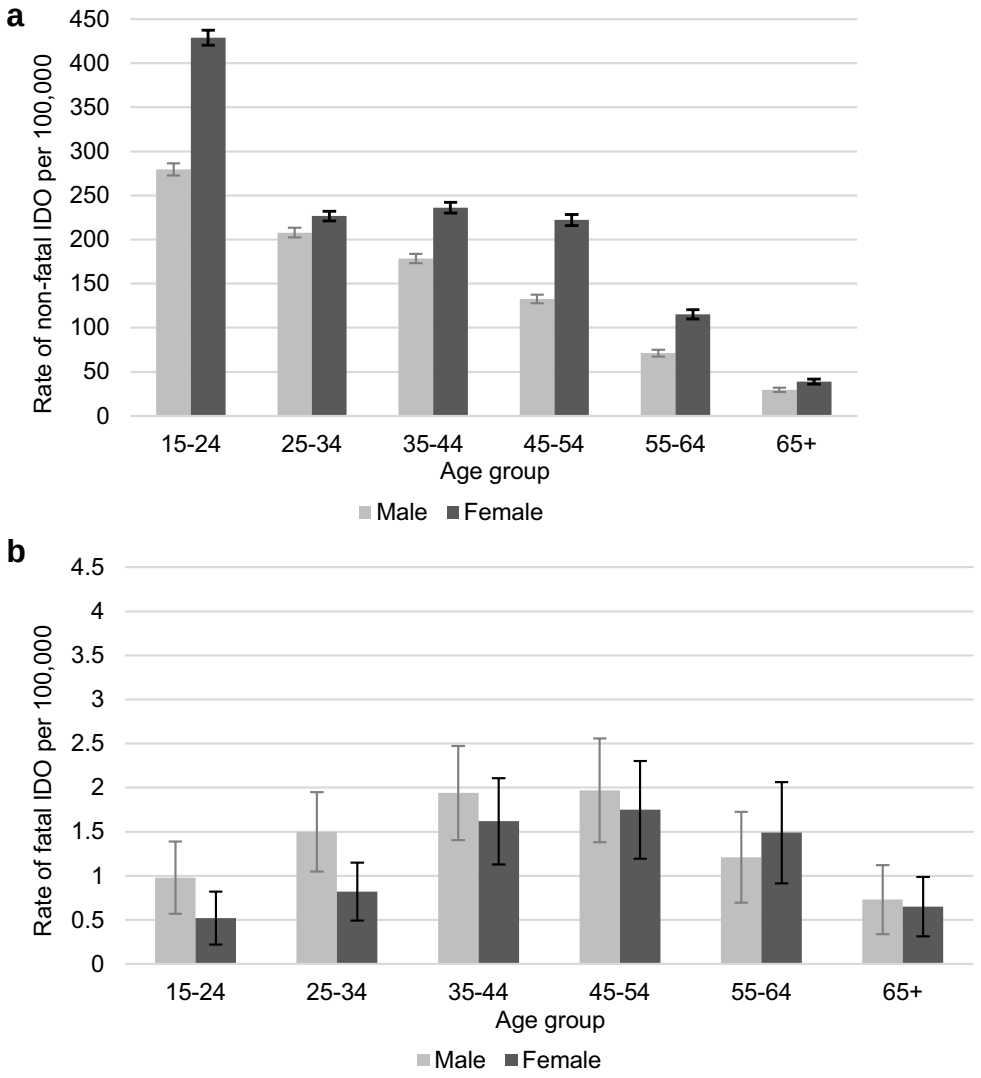

Fig. 1. Incidence of non-fatal (a) and fatal (b) intentional drug overdose per 100,000, by gender and age group with 95% confidence intervals, 2007–2014.

drug category (non-opioid analgesics). Opioid drugs were associated with over a 12-fold increased risk of death (CFRR = 12.9; 8.60–19.3, $p \leq 0.001$). Both antidepressant and illicit drug IDOs were over four times more likely to result in death (CFRR = 4.46; 3.06–6.49, $p \leq 0.001$ and CFRR = 4.02; 2.36–6.86, $p \leq 0.001$). Antiepileptic and anxiolytic drugs were associated with the lowest fatality risk ratios among the drug types examined (CFRR = 1.96; 1.17–3.29, $p = 0.010$ and CFRR = 2.08; 1.39–3.10, $p \leq 0.001$).

Examining fatality risk by gender, as shown in Table 2, the elevation in risk compared to the reference drug for females, was almost three times the risk elevation of males when tricyclic antidepressants were taken (CFRR = 23.6; 13.0–43.0, $p \leq 0.001$ vs. 9.02; 4.74–17.2,

Table 1
Case fatality risks and case fatality risk ratios by demographic and intentional drug overdose characteristics, 2007–2014.

Characteristics		All IDOs[1]	Fatal IDOs[2]	Case fatality risk%	Case fatality risk ratio (95% CI)
Gender	Female	37202	163	0.44 (0.37–0.51)	Reference
	Male	26993	201	0.74 (0.64–0.85)	1.70 (1.38–2.09) ***
Age group	15–24 years	18820	35	0.19 (0.12–0.25)	*Reference*
	25–44 years	29795	166	0.56 (0.47–0.64)	3.00 (2.08–4.31) ***
	≥45 years	15580	163	1.05 (0.88–1.21)	5.63 (3.91–8.11) ***
IDO type	Single drug IDO	32931	79	0.24 (0.19–0.29)	*Reference*
	Multiple drug IDO	31260	285	0.91 (0.8–1.02)	3.80 (2.96–4.88) ***
Number of drugs	1	32931	79	0.24 (0.19–0.29)	*Reference*
	2–5	30895	232	0.75 (0.65–0.85)	3.13 (2.43–4.04) ***
	≥6	365	53	14.5 (10.5–18.5)	60.5 (42.7–85.7) ***
Alcohol involvement	Yes	27656	151	0.55 (0.46–0.63)	*Reference*
	No	36539	213	0.58 (0.5–0.66)	1.07 (0.87–1.32)

Statistical significance = $p \leq 0.05$, ** = $p \leq 0.01$, *** = $p \leq 0.001$.
[1] All IDOs include all fatal and non-fatal IDOs within the study.
[2] Fatal IDOs include all IDOs which resulted in death within the study.

Table 2
The number and incidence rates of non-fatal and fatal intentional drug overdose where the drug caused death, and the associated case fatality risk and case fatality risk ratios, by gender, 2007–2014.

Drug	All IDOs[1]		Fatal IDOs[2]		Case fatality	
	Number	Rate per 100,000 (95% CI)	Number	Rate per 100,000 (95% CI)	Case fatality risk%	Case fatality risk ratio (95% CI)
Both genders						
Psycholeptics[3]	27970	77.6 (76.7–78.5)	166	0.46 (0.39–0.53)	0.59 (0.5–0.69)	2.41 (1.65–3.52) ***
Antipsychotics	6589	18.3 (17.8–18.7)	55	0.15 (0.11–0.19)	0.83 (0.61–1.06)	3.28 (2.14–5.02) ***
Anxiolytics	14778	41.0 (40.3–41.7)	78	0.22 (0.17–0.27)	0.53 (0.41–0.65)	2.08 (1.39–3.10) ***
Hypnotics and sedatives	13130	36.4 (35.8–37.1)	96	0.27 (0.21–0.32)	0.73 (0.58–0.88)	2.89 (1.94–4.31) ***
Benzodiazepines	24626	68.3 (67.5–69.2)	136	0.38 (0.31–0.44)	0.55 (0.46–0.65)	2.16 (1.48–3.16) ***
Psychoanaleptics[4]	13797	38.3 (37.6–38.9)	141	0.39 (0.32–0.45)	1.02 (0.85–1.19)	4.41 (3.03–6.42) ***
Antidepressants	13600	37.7 (37.1–38.4)	141	0.39 (0.33–0.46)	1.04 (0.86–1.21)	4.46 (3.06–6.49) ***
Tricyclics	1307	3.63 (3.43–3.83)	52	0.14 (0.10–0.18)	3.98 (2.88–5.08)	15.1 (9.90–23.2) ***
SSRIs	7669	21.3 (20.8–21.8)	56	0.16 (0.11–0.20)	0.73 (0.54–0.93)	3.15 (2.09–4.75) ***
Opioids	2830	7.85 (7.56–8.15)	79	0.22 (0.17–0.27)	2.79 (2.16–3.42)	12.9 (8.60–19.3) ***
Non-opioid analgesic	18031	50.0 (49.3–50.8)	*40*	0.11 (0.08–0.15)	0.22 (0.15–0.29)	*Reference*
Antiepileptics	4634	12.9 (12.5–13.2)	25	0.07 (0.04–0.10)	0.54 (0.32–0.76)	1.96 (1.17–3.29) **
Illicit drugs	3944	10.94 (11.3–10.9)	34	0.09 (0.06–0.13)	0.86 (0.57–1.16)	4.02 (2.36–6.86) ***
Males						
Psycholeptics	12205	68 (66.8–69.2)	87	0.48 (0.39–0.59)	0.71 (0.56–0.87)	1.98 (1.20–3.26) **
Antipsychotics	2763	15.4 (14.8–16)	20	0.11 (0.06–0.16)	0.72 (0.4–1.05)	1.89 (1.01–3.52) *
Anxiolytics	6744	37.6 (36.7–38.5)	39	0.22 (0.15–0.29)	0.58 (0.39–0.76)	1.58 (0.93–2.69)
Hypnotics and sedatives	5336	29.7 (28.9–30.5)	49	0.27 (0.19–0.35)	0.92 (0.66–1.18)	2.49 (1.47–4.21) ***
Benzodiazepines	10797	60.1 (59.0–61.3)	70	0.39 (0.30–0.48)	0.65 (0.49–0.8)	1.76 (1.06–2.91) *
Psychoanaleptics	4967	27.7 (26.9–28.5)	57	0.32 (0.23–0.40)	1.15 (0.84–1.45)	3.10 (1.87–5.15) ***
Antidepressants	4868	27.1 (26.3–27.9)	57	0.32 (0.23–0.40)	1.17 (0.86–1.48)	3.14 (1.89–5.22) ***
Tricyclics	472	2.63 (2.39–2.87)	17	0.09 (0.05–0.14)	3.6 (1.85–5.35)	9.02 (4.74–17.2) ***
SSRIs	2655	14.8 (14.2–15.4)	29	0.16 (0.10–0.22)	1.09 (0.69–1.5)	3.01 (1.73–5.24) ***
Opioids	1175	6.55 (6.16–6.93)	43	0.24 (0.17–0.31)	3.66 (2.54–4.78)	11.1 (6.47–19.1) ***
Non-opioid analgesic	6213	34.6 (33.7–35.5)	22	0.12 (0.07–0.17)	0.35 (0.2–0.51)	*Reference*
Antiepileptics	1805	10.1 (9.6–10.5)	12	0.07 (0.03–0.11)	0.66 (0.28–1.05)	1.69 (0.83–3.41)
Illicit drugs	2897	16.1 (15.5–16.7)	30	0.17 (0.11–0.23)	1.04 (0.66–1.41)	4.20 (2.27–7.76) ***
Females						
Psycholeptics	15615	85.9 (84.5–87.2)	79	0.43 (0.34–0.53)	0.51 (0.39–0.62)	2.91 (1.63–5.19) ***
Antipsychotics	3826	21 (20.4–21.7)	35	0.19 (0.13–0.26)	0.91 (0.61–1.22)	5.34 (2.89–9.85) ***
Anxiolytics	8034	44.2 (43.2–45.2)	39	0.21 (0.15–0.28)	0.49 (0.33–0.64)	2.77 (1.51–5.08) ***
Hypnotics and sedatives	7794	42.9 (41.9–43.8)	47	0.26 (0.18–0.33)	0.6 (0.43–0.78)	3.44 (1.87–6.35) ***
Benzodiazepines	13829	76 (74.7–77.3)	66	0.36 (0.27–0.45)	0.48 (0.36–0.59)	2.69 (1.50–4.83) ***
Psychoanaleptics	8830	48.6 (47.5–49.6)	84	0.46 (0.36–0.56)	0.95 (0.74–1.16)	6.32 (3.57–11.2) ***
Antidepressants	8732	48 (47.0–49.0)	84	0.46 (0.36–0.56)	0.96 (0.75–1.17)	6.37 (3.60–11.3) ***
Tricyclics	835	4.59 (4.27–4.91)	35	0.19 (0.13–0.26)	4.19 (2.77–5.61)	23.6 (13.0–43.0) ***
SSRIs	5014	27.6 (26.8–28.3)	27	0.15 (0.09–0.21)	0.54 (0.33–0.75)	3.32 (1.80–6.13) ***
Opioids	1655	9.10 (8.65–9.55)	36	0.20 (0.13–0.26)	2.18 (1.45–2.9)	15.4 (8.38–28.2) ***
Non-opioid analgesic	11758	64.6 (63.5–65.8)	18	0.10 (0.05–0.15)	0.15 (0.08–0.23)	*Reference*
Antiepileptics	2829	15.6 (15.0–16.1)	13	0.07 (0.03–0.11)	0.46 (0.2–0.71)	2.40 (1.19–5.15) *
Illicit drugs	1047	5.76 (5.40–6.11)	<5	–	–	3.29 (1.00–10.8) *

The case fatality risk ratio presented here is weighted and thus involves analyses whereby the drug of interest is counted as half within the reference drug group (e.g. non-opioid analgesics) and half within the drug group of interest. The process of weighting was performed to address the challenge of calculating case fatality risk ratios when multiple drugs caused death.
The case fatality risk ratios presented for both genders are adjusted for age.
Statistical significance = $p \leq 0.05$, ** = $p \leq 0.01$, *** = $p \leq 0.001$.
[1] All IDOs include fatal and non-fatal IDOs where the drug did not cause death.
[2] Fatal IDOs include fatal IDOs where the drug caused death.
[3] Psycholeptics are psychoactive drugs used to depress mental activity and include antipsychotics, anxiolytics, and hypnotics and sedatives.
[4] Psychoanaleptics are stimulant drugs including antidepressants, psychostimulants, nootropics anti-dementia drugs and combinations with psycholeptics.

$p \leq 0.001$), a disparity which was not apparent for female vs. male SSRI overdose IDO (CFRR = 3.32; 1.80–6.13, $p \leq 0.001$; 3.01; 1.73–5.24, $p \leq 0.001$). When illicit drugs were taken in IDO the risk of a fatal outcome is slightly elevated for males, compared to females (CFRR = 4.20; 2.27–7.76, $p \leq 0.001$ vs. 3.29; 1.00–10.8, $p \leq 0.001$). These patterns were essentially replicated when drugs involved in death were examined, although the magnitude of the difference was smaller; and also when we implemented alternative approaches for estimating the case fatality risk ratio, as reported in Supplementary Tables 5 and 6. Considering single drug IDOs, opioids were the drug type identified as most fatal in IDO (CFRR = 11.69; 3.73–36.7, $p \leq 0.001$), as highlighted in the Supplementary Table 3. The alternative means by which CFRR were calculated (double count and excluded in count) are presented, with very minor variations in estimates found, as reported in Supplementary Table 4).

Case fatality of individual drugs which caused death

Considering individual tricyclic antidepressant drugs, trimipramine or dosulepin were not found to confer any additional risk of death, compared to amitriptyline (CFRR = 0.93; 0.49–1.76, $p = 0.827$ and vs. 0.71; 0.18–3.02, $p = 0.662$ respectively), as reported in Table 3. Consuming the SSRI citalopram in IDO was associated with a 5-fold increased risk of death, compared to fluoxetine (CFRR = 5.26; 2.55–10.85, $p \leq 0.001$). Both opioid drugs morphine and oxycodone, were associated with significant increased risk of fatality following IDO, compared to the reference drug tramadol (CFRR = 4.16; 2.11–8.19, $p \leq 0.001$ vs. 3.94; 2.30–6.77, $p \leq 0.001$). This elevation in risk for both opioids examined, was higher for females than males, particularly so when morphine was consumed in IDO (CFRR = 6.67; 2.54–17.5, $p \leq 0.001$ vs. 2.85; 1.12–7.28, $p = 0.028$), as illustrated in Table 3.

Table 3
The number and incidence rates of non-fatal and fatal intentional drug overdose where individual drug caused death, and the associated case fatality risk and case fatality risk ratios, by gender, 2007–2014.

Drug	All IDOs [1]		Fatal IDOs [2]		Case fatality	
	Number	Rate per 100,000 (95% CI)	Number	Rate per 100,000 (95% CI)	Case fatality risk%	Case fatality risk ratio (95% CI)
Both genders						
Tricyclics						
Amitriptyline	784	2.18 (2.02–2.33)	37	0.10 (0.07–0.14)	4.72 (3.17–6.27)	*Reference*
Dosulepin	288	0.80 (0.70–0.89)	13	0.04 (0.02–0.06)	4.51 (2.01–7.02)	0.93 (0.49–1.76)
Trimipramine	58	0.16 (0.12–0.20)	<5	–	–	0.71 (0.18–3.02)
SSRIs						
Fluoxetine	1640	4.55 (4.33–4.78)	9	0.02 (0.01–0.04)	0.55 (0.18–0.91)	*Reference*
Citalopram	1279	3.55 (3.35–3.75)	41	0.11 (0.08–0.15)	3.21 (2.2–4.21)	5.26 (2.55–10.9) ***
Sertraline	1014	2.81 (2.64–2.99)	<5	–	–	0.74 (0.23–2.39)
Opioids						
Tramadol	1778	4.93 (4.70–5.17)	32	0.09 (0.06–0.12)	1.8 (1.16–2.44)	*Reference*
Oxycodone	287	0.80 (0.70–0.89)	24	0.07 (0.04–0.09)	8.36 (4.95–11.78)	3.94 (2.30–6.77) ***
Morphine	133	0.37 (0.31–0.43)	12	0.03 (0.01–0.05)	9.02 (3.81–14.23)	4.16 (2.11–8.19) ***
Males						
Tricyclics						
Amitriptyline	274	1.53 (1.34–1.71)	10	0.06 (0.02–0.09)	3.65 (1.34–5.96)	*Reference*
Dosulepin	106	0.59 (0.48–0.71)	6	0.03 (0.01–0.06)	5.66 (1.04–10.28)	1.41 (0.51–3.89)
Trimipramine	21	0.12 (0.07–0.17)	<5	–	–	1.26 (0.16–9.86)
SSRIs						
Fluoxetine	550	3.06 (2.80–3.33)	<5	–	–	*Reference*
Citalopram	449	2.50 (2.27–2.74)	20	0.11 (0.06–0.16)	4.45 (2.46–6.45)	5.90 (2.01–17.3) ***
Sertraline	323	1.80 (1.60–2.00)	<5	–	–	1.28 (0.29–5.28)
Opioids						
Tramadol	714	3.98 (3.68–4.28)	17	0.09 (0.05–0.14)	2.38 (1.23–3.54)	*Reference*
Oxycodone	137	0.76 (0.63–0.89)	11	0.06 (0.02–0.10)	8.03 (3.19–12.87)	3.11 (1.45–6.66) **
Morphine	80	0.45 (0.35–0.55)	6	0.03 (0.01–0.06)	7.5 (1.38–13.62)	2.85 (1.12–7.28) *
Females						
Tricyclics						
Amitriptyline	510	2.80 (2.56–3.05)	27	0.15 (0.09–0.21)	5.29 (3.26–7.33)	*Reference*
Dosulepin	182	1.00 (0.85–1.15)	7	0.04 (0.01–0.07)	3.85 (0.94–6.75)	0.73 (0.32–1.68)
Trimipramine	37	0.20 (0.14–0.27)	<5	–	–	0.51 (0.69–3.76)
SSRIs						
Fluoxetine	1090	6.0 (5.63–6.36)	5	0.03 (0.00–0.05)	0.46 (0.05–0.87)	*Reference*
Citalopram	830	4.56 (4.25–4.88)	21	0.12 (0.07–0.17)	2.53 (1.43–3.63)	4.69 (1.76–12.5) **
Sertraline	691	3.80 (3.51–4.09)	<5	–	–	0.32 (0.04–2.70)
Opioids						
Tramadol	1064	5.85 (5.49–6.21)	15	0.08 (0.04–0.13)	1.41 (0.68–2.14)	*Reference*
Oxycodone	150	0.82 (0.69–0.96)	13	0.07 (0.03–0.11)	8.67 (3.86–13.47)	5.06 (2.33–11.0) ***
Morphine	53	0.29 (0.21–0.37)	6	0.03 (0.01–0.06)	11.3 (2.08–20.6)	6.67 (2.54–17.5) ***

The case fatality risk ratio presented here is weighted and thus involves analyses whereby the drug of interest is counted as half within the reference drug group (non-opioid analgesics) and half within the drug group of interest. The process of weighting was performed to address the challenge of calculating case fatality risk ratios when multiple drugs caused death.
The case fatality risk ratios presented for both genders are adjusted for age.
Statistical significance = $p \leq 0.05$, ** = $p \leq 0.01$, *** = $p \leq 0.001$.
[1] All IDOs include fatal and non-fatal IDOs where the drug did not cause death.
[2] Fatal IDOs include fatal IDOs where the drug caused death.

Discussion

Main findings and interpretation

To our knowledge this is the first study which estimated case fatality risk associated with IDOs involving multiple drug types, which we examined using robust data from two national routinely collected datasets. We found that tricyclic antidepressants and opioid drugs are associated with a significantly increased risk of death following IDO, and this risk was greater in females than males when these drugs were taken. Male gender, increasing age and multiple drug use were found to be strong predictors of fatality in IDO.

The consumption of tricyclic antidepressants in IDO was linked with an approximate 15-fold increased risk of subsequent death versus non-opioid analgesics. The findings of this study builds upon other research that has attributed a high level of toxicity to tricyclic antidepressants (Hawton et al., 2010). The UK National Institute for Health and Care Excellence (NICE) clinical guideline (CG133) 2011, recommends "When prescribing drugs for associated mental health conditions to people who self-harm, take into account the toxicity of the prescribed drugs in overdose…In particular, do not use tricyclic antidepressants, such as dosulepin, because they are more toxic" (NICE, 2011). However, Carr et al., 2016 identified that approximately one in ten patients who have recently harmed themselves continue to be prescribed these drugs (Carr et al., 2016). Subsequent NICE pathway guidelines continue to emphasize the risk of IDO with tricyclic antidepressants in persons with identified suicide risk (NICE, 2018). Considering the risks of fatal overdose which are associated with tricyclic antidepressants, action in addition to recommendations is perhaps needed in order to protect patients at risk of overdosing with these drugs. Within this study no individual tricyclic antidepressant stood out as attributing excessive case fatality which is dissimilar to previous research which identified dosulepin and doxepin as more toxic than other tricyclic drugs (Hawton et al., 2010), which could be due to the involvement of small numbers of individual tricyclics in fatal IDOs within this study. However, the identification of the SSRI citalopram as five times more toxic than the reference SSRI drug (fluoxetine) builds upon the finding of excessive risk associated with this particular drug by Hawton et al., 2010. Notwithstanding the evidence base recommending SSRI prescribing as a first line antidepressant treatment (NICE, 2018), the

fatality risk associated with citalopram requires clinical consideration when the patient has an identified risk of suicide.

Despite having a relatively low rate of involvement in IDO among the drug types examined, opioids were associated with a 12-fold increased risk of death following IDO, versus non-opioid analgesics. The incidence rate of IDOs involving opioid drugs identified in this study (7.85 per 100,000; 95% CI: 7.56–8.15) is similar to the most recent national prevalence estimates of opioid users in Ireland, as of 2014, (6.18 per 100,000; 95% CI: 6.09–6.98). The OECD reported that the recent increases in opioid deaths in Ireland was among the most pronounced of the 25 countries examined, whereby the rate per million inhabitants stands at approximately one third that of the USA (43.5 versus 131.0 per million) (OECD, 2019), highlighting a significant threat to public health. The fatality of an opioid overdose has been found to increase if the overdose involves the co-ingestion of other drugs (predominantly benzodiazepines) (Sgarlato & deRoux, 2015), the individual had a prescription for opioids within 30 days of death (Austin, Proescholdbell, Creppage & Asbun, 2017), the patient was on a high dose of opioid prescription (Bohnert et al., 2011; Ilgen et al., 2016), and if the individual had previous opioid overdose hospitalization (Kelty & Hulse, 2017). One commonality between these precipitating factors is the involvement of a healthcare professional, signaling an opportunity for intervention. However, the evidence base for measures to reduce opioid overdose deaths is not yet comprehensive. Some emerging evidence illustrates effectiveness for naloxone distribution interventions (McDonald & Strang, 2016) and treatments involving medications for opioid use disorder (Sordo et al., 2017). A systematic review by Frank et al., 2017 also found some evidence, albeit of low quality, supporting opioid tapering (reducing opioid dosage over time) in an environment whereby the patient is monitored for any adverse effects of dose-tapering (Frank et al., 2017). Considering the high potential for fatality following opioid IDO and the established increase in opioid deaths, additional research, of greater quality, is needed to examine the potential impact, including dangers, associated with risk reduction measures.

Benzodiazepines are among the most frequently used drugs taken in IDO, yet the risk of death following IDO involving these drugs was among the lowest of the drug groups examined. This finding, albeit with a weaker observed association, concurs with findings reported from other research (Geulayov et al., 2018). Measures identified to reduce repeat or fatal IDO with benzodiazepines include: conducting an assessment of suicide risk with patients prior to prescribing a benzodiazepine (Dodds, 2017), and lowering benzodiazepine dosage (Okumura & Nishi, 2017). Whilst dose-tapering, in conjunction with non-pharmacological interventions are effective benzodiazepine discontinuation measures, it is not known whether reduction strategies could result in potential adverse effects for patients, warranting further research (Canadian Agency for Drugs & Technologies in Health, 2015). Follow-up and monitoring of patients who receive potentially toxic drugs for specific indications such as depression and other mental illnesses is a more practical recommendation in the absence of further evidence. Another outstanding key factor warranting further research is the frequency with which benzodiazepines are being prescribed with other potentially toxic medications, including opioids, as this can increase the risk of a fatal outcome.

In line with the wider literature on self-harm and suicide, the incidence of non-fatal IDO reported in this study were higher for females (Finkelstein et al., 2016) although risk of dying by IDO was higher for males (Jansen, Buster, Zuur & Das, 2009). This paradox is often attributed to gender-related differences in method choice (Cibis et al., 2012), intent (Freeman et al., 2017) or the disproportionate gender distribution of depressive disorders (Alonso et al., 2004). The increased fatality for males identified in this study, which examines IDO only, suggests that factors excluding method choice are accountable for differences in case fatality between genders. This study identifies variability in drug types taken by males and females as impacting upon risk of death following IDO. However, as female fatality risk was elevated for all drug groups examined except illicit drugs, drug type is unlikely to account for the greater risk of a fatal outcome following overdose among males. To this end, more research is needed to elucidate the mechanisms that explain gender differences in fatality risk following IDO.

Fatal IDO cases in this study were older than non-fatal cases. Lower case fatality in younger age has been attributed to better overall health status, lesser suicidal intent and increased chance of survival, compared to older persons (Jansen et al., 2009). Conversely, accessibility to prescribed medications and better knowledge of the lethality of medications among older people has been used to explain their increased risk of fatality following IDO (Schmidtke et al., 2004). Considering the finding by Chen et al., 2009 that the effect of age on fatality is stronger for poisoning compared to other methods of self-harm (Chen et al., 2009), the link between growing age and increasing fatality, identified by this study, is an important consideration for the prevention of fatal IDO in older persons. Prescribers should remain cognisant of the medication load of older patients and monitor for and respond to indicators of drug misuse within this subgroup. In particular, prescribing of drugs including those with established toxicity, should be reviewed before long term-use is established to ensure patient safety in which the therapeutic effects are balanced against the risk of potential harm from such drugs (Bedson et al., 2019).

The involvement of multiple drugs in almost half of all non-fatal IDOs and approximately 80% of fatal IDOs identified in this study is significantly greater than found in previous comparative studies (Finkelstein et al., 2016; HRB, 2015; Vancayseele et al., 2016). Considering that the fatality of an IDO increases significantly as the number of drugs used in combination increases, the importance of restricting or avoiding multiple drug prescribing, when possible, is indicated by our findings. As successful suicide prevention required multiple level interventions, such means restriction measures should also be accompanied by treatments at individual level, to be provided by the mental health and allied services, including patient education, effective pharmacological and psychological treatments (Zalsman et al., 2016).

Strengths and limitations

Our study has important strengths, including the use of robust national data covering an eight-year period. The utilization of two datasets with full national coverage, capturing all non-fatal hospital-based IDO presentations and all deaths due to IDO, respectively, is a unique strength of this study. The examination of case fatality of both single and multiple drug IDOs, and the novel analytical approach used to test case fatality estimates paves the way for future researchers to expand beyond examinations of fatality following single drug overdose. Furthermore, the examination of drugs identified as being a cause of or involved in death (as determined by the Coroner) adds to the robustness of our findings and strengthens the conclusions drawn.

The results of this study should be interpreted in the context of its limitations. Owing to the absence of a common unique patient identifier in both datasets examined it was not possible to perform data linkage. Thus, the case fatality risks reported represent an approximation of fatality risk between unlinked non-fatal and fatal IDO cases. Confounding by indication is an important consideration when interpreting the study findings, as persons taking medications may have an initial higher risk of death prior to taking these drugs, due to the pre-existing physical or mental illnesses for which they are taking these drugs. This study examined non-fatal IDO episodes that resulted in hospital presentation, thereby excluding those that entailed general practice presentation only or those that go untreated by any healthcare professional. The NSHRI collects only information pertaining to treatment allocated in the emergency department, and it is therefore possible that persons who presented following non-fatal IDO may have subsequently died post-discharge or following recommended next care.

Information collected on drugs used and quantity of tablets consumed in IDO was self-reported by the presenting individual, which may be subject to inaccuracy; however, these data are supplemented by ambulance service records, hospital medical records and toxicology reports where present. Finally, the certification of a drug as causal to death is established by the Coroner, using information obtained from the State Pathologist and State Laboratory for Human Toxicology, whereby the decision is based on the interoperation of the Coroner and thus may be subjective and not uniform across coronial districts.

Conclusion

Male gender, increasing age and multiple drug use were associated with fatal IDO. Tricyclic antidepressants and opioids were associated with significant elevations in risk of a fatal outcome following IDO. These findings add to the current evidence regarding the risk and potential adverse outcomes associated with these drugs, which informs safe and appropriate prescribing, where clinicians consider the fatality risk of drugs when determining treatment for patients at risk of self-harm or who have previously harmed themselves.

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Conflict of Interest Statement

Caroline Daly, Eve Griffin, Roger T. Webb, Paul Corcoran, Ivan J. Perry and Ella Arensman have no conflicts of interest to disclose. Darren M. Ashcroft has, outside of the submitted work, received grants from Abbvie, Almirall, Celgene, Eli Lilly, Novartis, UCB and the Leo Foundation.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.drugpo.2019.102609.

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