Drug poisoning deaths among women in Ireland

A thesis submitted to the RCSI University of Medicine and Health Sciences, for the degree of Doctor of Philosophy

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Declaration

I declare that this thesis, which I submit to the RCSI for examination in consideration of the award of a higher degree of Doctor of Philosophy is my own personal effort. Where any of the content presented is the result of input or data from a related collaborative research programme this is duly acknowledged in the text such that it is possible to ascertain how much of the work is my own. I have not already obtained a degree in the RSCI or elsewhere on the basis of this work. Furthermore, I took reasonable care to ensure that the work is original, and, to the best of my knowledge, does not breach copyright law, and has not been taken from other sources except where such work has been cited and acknowledged within the text.

Signed: 

Student number: 17168783

Date: 31st January 2022

TABLE OF CONTENTS

Declaration 2

Acronyms and Abbreviations 10

Acknowledgements 12

Dedication 13

List of Figures 14

List of Tables 15

Abstract 17

Papers for Consideration 19

Paper one: Drug poisoning deaths among women: a scoping review 19

Paper two: Trends in drug poisoning deaths, by sex, in Ireland: a repeated cross-sectional study from 2004 to 2017. 19

Paper three: A repeated cross-sectional study of factors associated with pregabalin-positive poisoning deaths in Ireland. 20

Paper four: Comparing characteristics of suicide to non-suicide drug poisoning deaths, by sex, in Ireland. 20

Oral presentations 21

Poster presentation 24

Chapter 1: Introduction 25

1.1 Women and drug poisoning deaths 26

1.2 Biological differences between men and women 29

1.3 Representation of women in clinical drug trials 30

1.4 Why public health data should be stratified by sex 31

1.5 Rationale for the thesis 32

1.6 Thesis aims and objectives 37

1.7 Data sources 38

1.7.1 The National Drug-Related Deaths Index (NDRDI) 38

1.7.2 The Health Service Executive (HSE) Primary Care Reimbursement Services (PCRS) 42
1.8 Method 43
1.9 Thesis outline 44
1.10 References 46
Chapter 2: Drug poisoning deaths among women: a scoping review 55
2.1 Abstract 56
2.2 Introduction 57
2.2.1 Objectives 58
2.3 Method 58
2.3.1 Stage 1: Identify the research question 58
2.3.2 Stage 2: Identify and retrieve relevant items 59
2.3.3 Stage 3: Study selection (Figure 2.1) 61
2.3.4 Stage 4: Charting the data 61
2.3.5 Stage 5: Collating, summarising, and reporting 61
2.3.6 Stage 6: Consultation exercise 62
2.4 Results 62
2.4.1 Study design 62
2.4.2 Drugs involved in poisoning deaths among women 63
2.4.3 Individual characteristics 63
2.4.4 External factors 72
2.5 Discussion 73
2.5.1 Gaps in research and considerations for policy and practice 74
2.5.2 Strengths and limitations 75
2.5.3 Conclusion 76
2.5.4 Acknowledgements 76
2.6 References 77

Chapter 3: Trends in drug poisoning deaths, by sex, in Ireland: a repeated cross-sectional study from 2004 to 2017 87
3.1 Abstract 88
3.2 Introduction 90
3.3 Methods 91
3.3.1 Patient and public involvement 91
3.3.2 Data sources 92
3.3.3 Study variables 93
3.3.4 Statistical analysis 94
3.4 Results 95
3.4.1 All drug poisoning deaths 95
3.4.2 CNS depressant drugs 96
3.4.3 Prescription opioids 96
3.4.4 Benzodiazepines 96
3.4.5 Antidepressants 99
3.4.6 Alcohol 99
3.4.7 Cocaine 99
3.4.8 Heroin 100
3.5 Discussion 103
3.5.1 Summary of findings 103
3.5.2 Clinical and policy implications 107
3.5.3 Strengths and limitations 110
3.5.4 Conclusion 111
3.5.5 Acknowledgements 111
3.6 References 112
Chapter 4: A repeated cross-sectional study of factors associated with pregabalin-positive poisoning deaths in Ireland 120
4.1 Abstract 121

4.2 Introduction 122
4.3 Methods 123
4.3.1 Study design, setting and population 123
4.3.2 Data sources 124
4.3.3 Study variables 124
4.3.4 Statistical analysis 125
4.4 Results 128
4.4.1 Description of study population 128
4.4.2 Factors associated with PPPD 128
4.4.3 Gender specific analysis 129
4.4.4 Toxicology 129
4.5 Discussion 130
4.5.1 Summary of findings in context of previous studies 130
4.5.2 Implications for treatment and prescribing practices 132
4.5.3 Policy and legislation 133
4.5.4 Strengths and limitations 133
4.5.5 Future research 134
4.5.6 Conclusion 134
4.6 References 136
Chapter 5: Comparing characteristics of suicide to non-suicide drug poisoning deaths, by sex, in Ireland 141
5.1 Abstract 142
5.2 Background 143
5.3 Methods 144
5.3.1 Study design 144
5.3.2 Data source and population 145
5.3.3 Study variables 146

5.3.4 Statistical analysis 148
5.4 Results 149
5.4.1 Description of study population 149
5.4.2 Analysis stratified by sex 150
5.4.3 Drugs implicated in the deaths 152
5.5 Discussion 158
5.5.1 Summary of findings in the context of previous studies 158
5.5.2 Drugs implicated in the deaths 161
5.5.3 Policy and practice implications 163
5.5.4 Strengths and limitations 164
5.6 Conclusion 165
5.6.1 Acknowledgement 165
5.7 References 166
Chapter 6: Discussion 175
6.1 Summary of findings 175
6.2 Strengths and limitations 179
6.2.1 Key strengths 179
6.2.2 Key limitations 180
6.3 Overall health research impacts 184
6.3.1 Research-related impact 184
6.3.2 Policy impact 186
6.3.3 Health service delivery impact 189
6.3.4 Societal impact 192
6.4 Possible future research 193
6.5 Conclusion 197
Chapter 7: References from narrative part of thesis 199
Chapter 8: Appendices 212

Appendix 1.1 Data sources for repeated cross-sectional studies..... 212

Appendix 2.1 Drug poisoning deaths among women: scoping review protocol .. 218

Appendix 2.2 Supplementary Table A Characteristics of Primary Studies Included (*n* = 50) 227

Appendix 2.3 Supplementary Table B Characteristics of Secondary Research Included (*n* = 11)..... 239

Appendix 2.4 Supplementary Table C MEDLINE search strategy 243

Appendix 2.5 Lisbon addiction conference poster - Drug poisoning deaths among women: a scoping review..... 246

Appendix 3.1 Drugnet Ireland article: Trends in drug poisoning deaths, by sex, in Ireland: a repeated cross-sectional study, 2004–2017..... 247

Appendix 4.1 Supplementary Table D: Pearson correlation coefficient between the main other drugs present on toxicology and covariates ‘a history of opioid misuse’ and ‘in receipt of treatment for problematic drug use’ 250

Appendix 4.2 Drugnet Ireland article: Has an increase in the dispensing of pregabalin influenced poisoning deaths in Ireland? 251

Appendix 4.3 Drugnet Ireland article: A repeated cross-sectional study of factors associated with pregabalin-positive poisoning deaths in Ireland..... 256

Appendix 4.4 Supplementary Table E. Sensitivity test: Unadjusted and adjusted ORs (95% CI) of factors associated with poisoning deaths with and without pregabalin on toxicology, 2013 to 2016 with ‘unknowns’ recorded as system missing..... 261

Appendix 5.1 Supplementary Table. Sensitivity analysis MODEL 1: Unadjusted and adjusted ORs (95% CI) comparing characteristics and factors for coronial verdict of suicide drug poisoning deaths verses non-suicide drug poisoning deaths, overall and stratified by sex, NDRDI data 2015 to 2017 inclusive (n=1114) 262

Appendix 5.2 Supplementary Table. Sensitivity analysis: Unadjusted and adjusted ORs (95% CI) comparing drugs implicated in coronial verdict of suicide drug poisoning deaths verses non-suicide drug poisoning deaths, overall and stratified by sex, NDRDI data 2015 to 2017 inclusive (n=1114) 264

Appendix 5.3: Death investigation process for drug poisoning deaths in Ireland 266

Acronyms and Abbreviations

AAPC: Average Annual Percentage Change

APC: Annual Percentage Change

ASMR: Age Standardised Mortality Rates

AOR: Adjusted Odds Ratio

ASR: Age Standardised Rates

CDC: Centers for Disease Control and Prevention

CEO: Chief Executive Officer

CI: Confidence Intervals

CNS: Central Nervous System

Cor: Coronial

CSO: Central Statistics Office

CTL: Central Treatment List

EMCDDA: European Monitoring Centre for Drugs and Drug Addiction

FDA: Food and Drug Administration

GDPR: General Data Protection Regulation

GMS: General Medical Services

GP: General Practitioner

HIPE: Hospital In-Patient Enquiry scheme

HPO: Healthcare Pricing Office

HPRA: Health Products Regulatory Authority

HRB: Health Research Board

HSE: Health Service Executive

IMC: Irish Medical Council

IQR: Interquartile Range

MMP: Medicines Management Programme

NDRDI: National Drug-Related Deaths Index

NFSN: National Family Support Network

NOSP: National Office for Suicide Prevention

NSDPD: Non-Suicide Drug Poisoning Death

OAT: Opioid Agonist Treatment

OR: Odds Ratio

PCRS: Primary Care Reimbursement Scheme

PPPD: Pregabalin-Positive Poisoning Death

PNPD: Pregabalin-Negative Poisoning Death

REITOX: Réseau Européen d'Information sur les Drogues et les Toxicomanies

SDPD: Suicide Drug Poisoning Death

SSA: Society for the Study of Addiction

SUAB: Substance Use and Associated Behaviours Research Group

SUD: Substance Use Disorder

UNICRI: United Nations Interregional Crime and Justice Research Institute

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Thank you to my parents Johnny and Bertie, now deceased, who always placed great value on education. I know they would be proud. To my siblings, Maura, David, Gerard, Ruth, Sinead and Raymond, and my extended family, especially Ailbhe and Olivia for your support and encouragement. In particular, I would like to acknowledge my sister-in-law Mari who died 19th October 2021. Mari's positive attitude to life, her compassion, enthusiasm and driving ambition was an inspiration to us all. A special thank you to my sister Jackie for ensuring I switched off from PhD work, HRB work, and busy family life and slowed down for our weekends together, a precious time.

Lastly, my immediate family deserves endless gratitude. To Brendan, Chloe, Jack, and Leah, without your tremendous understanding and encouragement over the past four years, it would not have been possible for me to undertake this project. Thank you!

Dedication

The thesis is dedicated to my beautiful sister Jackie, who died 31st December 2021.

Thank you for showing me by example what is truly valuable in life.

List of Figures

Figure 1.1 A Public Health Approach. Source: Centers for Disease Control and Prevention (CDC) 26

Figure 1.2 Trends in drug poisoning deaths using the EMCDDA inclusion criteria and the NDRDI inclusion criteria, 2008 to 2017 34

Figure 1.3 Suicide and non-suicide drug poisoning deaths, by sex, (2015-2017 combined), n = 1114 35

Figure 1.4 Age-specific rates of drug poisoning deaths among men, NDRDI 2004 to 2017 36

Figure 1.4 Age-specific rates of drug poisoning deaths among women, NDRDI 2004 to 2017 36

Figure 2.1 Selection of sources of evidence 60

Figure 3.1 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-GMS; 2004 to 2017. 98

Figure 3.2 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-GMS; 2004 to 2017..... 98

Figure 4.2.1 Relationship between the number of pregabalin items dispensed and pregabalin-positive poisoning deaths, NDRDI 2013 to 2016 253

List of Tables

Table 2.1 Characteristics of evidence from 61 publications included 66

Table 3.1 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 101

Table 3.2 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 102

Table 3.3 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..... 103

Table 4.1 Factors associated with PPPD, 2013 to 2016 (n=1489) 126

Table 4.2 Main other drugs on toxicology reports associated with PPPD, with unadjusted odds ratios for men and women presented separately, 2013 to 2016 (n=1489)..... 127

Table 5.1 Unadjusted and adjusted ORs (95% CI) comparing characteristics and factors for suicide drug poisoning deaths (SDPD) [n=240] versus non-suicide drug poisoning deaths (NSDPD) [n=874], NDRDI data 2015 to 2017 inclusive [n=1114] 151

Table 5.2 Unadjusted and adjusted ORs (95% CI) comparing characteristics and factors for suicide drug poisoning deaths (SDPD) [n=240] versus non-suicide drug poisoning deaths (NSDPD) [n=874], stratified by sex, NDRDI data 2015 to 2017 inclusive [n=1114] 154

Table 5.3 Unadjusted ORs (95% CI) of drugs implicated in drug poisoning deaths (suicide drug poisoning deaths (SDPD) [n=240] verses non-suicide drug poisoning deaths [n=874] (NSDPD)), overall and stratified by sex, NDRDI data 2015 to 2017 inclusive [n=1114] 156

Supplementary Table 1.1 Data sources characteristics 216

Appendix 2.4 Supplementary Table C MEDLINE search strategy 243

Table 4.2.1 PCRS Pregabalin dispensing frequency, number of poisoning deaths with a pregabalin positive toxicology and % of deaths related to PCRS dispensing BY year, 2013-2016 252

Table 4.3.1 Factors significantly associated with PPPD, 2013 to 2016 (n=1489)... 260

Abstract

More men than women die of drug poisoning deaths. However, due to biological, social, and psychological differences between men and women it is important for evidence to be stratified by sex so that effective policy and practice responses to drug poisoning deaths can be developed for both men and women. The majority of data on drug poisoning deaths is aggregated data; therefore, as these deaths are dominated by men, specific risk factors relevant to women may be masked. The overarching aim of this research is to explore what is known about poisoning deaths among women, identify gaps in knowledge and contribute to evidence-based practice. Specific objectives include to: (1) investigate the extent of existing knowledge on drug poisoning deaths among women; (2) explore trends in drug poisoning deaths in Ireland stratified by sex; identify specific drugs/drug groups involved and if they differ by sex; (3) explore factors associated with an emerging drug, pregabalin, in drug poisoning deaths in Ireland, by sex and (4) explore factors associated with suicide drug poisoning deaths in Ireland among women relative to men.

The scoping review highlights the current dearth of knowledge on factors associated with drug poisoning deaths among women. An overview of trends in drug poisoning deaths over a fourteen-year period, stratifying by sex, found multiple CNS depressant drugs to have a significant role in drug poisoning deaths among women. In a study examining factors associated with pregabalin positive drug poisoning deaths, women who died of a drug poisoning death where pregabalin, a CNS depressant drug, was present on toxicology were 3 times more likely than men to have ≥2 other CNS depressant drugs present. Finally, a study examining characteristics associated with suicide drug poisoning deaths found consistent findings in relation to associated factors, with small variation in magnitude of effects, for both men and women. However, ≥2 CNS depressant drugs were found to be associated with decreased odds of the death being a suicide relative to a non-suicide drug poisoning death for men only.

In summary, this thesis demonstrates a significant association between multiple CNS depressants and drug poisoning deaths among women. The findings indicate the need for increased education among prescribers and users on differences between sexes in relation to drug metabolism and actions, and practical

implications are suggested to facilitate more appropriate and mixed treatment options for people who use drugs.

Papers for Consideration

Paper one: Drug poisoning deaths among women: a scoping review

Published: Yes

Journal: Journal of Studies on Alcohol and Drugs

Journal impact factor: 2.616

Quartiles: Q1

Citation metrics: 5 citations

Reference: Lynn E, Doyle A, Keane M, Bennett K, Cousins G. (2020) Drug poisoning deaths among women: a scoping review. *Journal of Studies on Alcohol and Drugs*. 81(5), 543-55. doi:10.15288/jsad.2020.81.543

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

Published: Yes

Journal: BMJ Open

Journal impact factor: 2.496

Quartiles: Q1

Citation metrics: 1 citation

Reference: Lynn E, Cousins G, Lyons S, Bennett K.E. (2021). Trends in drug poisoning deaths, by sex, in Ireland: a repeated cross-sectional study from 2004 to 2017. *BMJ Open*. 11:e048000. doi:10.1136/bmjopen-2020-048000

Paper three: A repeated cross-sectional study of factors associated with pregabalin-positive poisoning deaths in Ireland.

Published: Yes

Journal: Drug and Alcohol Dependence

Journal impact factor: 3.951

Quartiles: Q1

Citation metrics: 11 citations

Reference: Lynn E, Cousins G, Lyons S, Bennett K.E. (2020). A repeated cross-sectional study of factors associated with pregabalin-positive poisoning deaths in Ireland. *Drug and Alcohol Dependence*. 206, 107741. doi:10.1016/j.drugalcdep.2019.107741.

Paper four: Comparing characteristics of suicide to non-suicide drug poisoning deaths, by sex, in Ireland.

Published: Yes

Journal: Journal of Affective Disorders

Journal impact factor: 4.837

Quartiles: Q1

Citation metrics: published online 21 March 2022

Reference: Lynn E, Cousins G, Lyons S, Bennett K.E. (2022). Comparing characteristics of suicide to non-suicide drug poisoning deaths, by sex, in Ireland. *Journal of Affective Disorders, 306,* 80-89. doi:10.1016/j.jad.2022.03.030

Oral presentations

- **Lynn E**. Using toxicology results to highlight public health issues: including factors associated with pregabalin-positive poisoning deaths in Ireland. Students undertaking a diploma course in Drug and Alcohol Studies, University of Limerick. Dublin. 16 Jan 2019

- **Lynn E**., Cousins G., Lyons S. Bennett K.E. A repeated cross-sectional study of factors associated with pregabalin-positive poisoning deaths in Ireland. Directorate of Health Information and Evidence, Health Research Board. Dublin. 20 June 2019.

- **Lynn E**., Cousins G., Lyons S. Bennett K.E. A repeated cross-sectional study of factors associated with pregabalin-positive poisoning deaths in Ireland. Health Service Executive Medicines Management Programme. Dublin. 29 July 2019.

- **Lynn E**., Cousins G., Lyons S. Bennett K.E. Provisional data on trends in drug poisoning deaths and use of coronial data to examine factors associated with pregabalin-positive poisoning deaths in Ireland. The Coroner's Society of Ireland. Monaghan. 6 Sept 2019.

- **Lynn E**. Using toxicology results to highlight public health issues: including factors associated with pregabalin-positive poisoning deaths in Ireland. Students undertaking a diploma course in Drug and Alcohol Studies, University of Limerick. Dublin. 2 Oct 2019

- **Lynn E**., Cousins G., Lyons S. Bennett K.E. A repeated cross-sectional study of factors associated with pregabalin-positive poisoning deaths in Ireland. Lisbon Addiction conference. Lisbon. 23 Oct 2019

- **Lynn E**., Cousins G., Lyons S. Bennett K.E. A repeated cross-sectional study of factors associated with pregabalin-positive poisoning deaths in Ireland. NDRDI Steering Committee. Dublin. 15 Nov 2019.

- **Lynn E**., Cousins G., Lyons S. Bennett K.E. A repeated cross-sectional study of factors associated with pregabalin-positive poisoning deaths in Ireland. Health Products Regulatory Agency (HPRA) Dublin. 22 Jan 2020.

- **Lynn E**, Cousins G, Lyons S, Bennett K.E. Trends in drug poisoning deaths, by sex, in Ireland: a repeated cross-sectional study from 2004 to 2017. Department of Health Drugs Policy and Social Inclusion Unit. Dublin. 30 Jan 2020.

  Lynn E, Cousins G, Lyons S, Bennett K.E. A repeated cross-sectional study of factors associated with pregabalin-positive poisoning deaths in Ireland. Irish Medical Council, Dublin. 11 March 2020

- **Lynn E**, Cousins G, Lyons S, Bennett K.E. A repeated cross-sectional study of factors associated with pregabalin-positive poisoning deaths in Ireland. Irish College of General Practitioner's 'Addiction Management in Primary Care Certificate Course workshop'. [online] 23 May 2020

- **Lynn E**, Cousins G, Lyons S, Bennett K.E. A repeated cross-sectional study of factors associated with pregabalin-positive poisoning deaths in Ireland. Irish College of General Practitioner's webinar. Topic of webinar 'Benzodiazepines and Pregabalin Prescribing - How can we improve?'. [online] 1 July 2020

- **Lynn E**, Cousins G, Lyons S, Bennett K.E. Trends in drug poisoning deaths, by sex, in Ireland: a repeated cross-sectional study from 2004 to 2017. Irish College of General Practitioner's 'Addiction Management in Primary Care Certificate Course workshop'. [online] 16 Oct 2020

- **Lynn E**. Examples of using the data to influence both policy and practice. InfAct 1st European Health Information Course. [online] 29 Oct 2020

- **Lynn E**, Cousins G, Lyons S, Bennett K.E. A repeated cross-sectional study of factors associated with pregabalin-positive poisoning deaths in Ireland. Society for the Study of Addiction (SSA) PhD symposium. [online] 4 Nov 2020

- **Lynn E**, Cousins G, Lyons S, Bennett K.E. Trends in drug poisoning deaths, by sex, in Ireland and the impact on policy and practice. *National Oversight Committee*, chaired by the Minister with responsibility for the National Drugs Strategy. [online] 4 Dec 2020

- **Lynn E**, Cousins G, Lyons S, Bennett K.E. Trends in drug poisoning deaths by sex, in Ireland, 2004 to 2017. RSCI Research Day. [online] 10 March 2021 - Joint winner for oral presentation in the Clinical and Applied Research section of the RCSI Research Day

- **Lynn E**. Using toxicology results to highlight public health issues: including factors associated with pregabalin-positive poisoning deaths in Ireland. Students undertaking a diploma course in Drug and Alcohol Studies, University of Limerick. Dublin. [online] 15 Apr 2021

- **Lynn E**, Cousins G, Lyons S, Bennett K.E. Trends in drug poisoning deaths by sex, in Ireland, 2004 to 2017. Substance Use and Associated Behaviours Research Group (SUAB) PhD symposium. [online] 21 April 2021

- **Lynn E**, Cousins G, Lyons S, Bennett K.E. Trends in drug poisoning deaths by sex, in Ireland, 2004 to 2017. EMCDDA Expert meeting on the epidemiological indicator: Drug-related deaths. [online] 30 Sept 2021

- **Lynn E**, Cousins G, Lyons S, Bennett K.E. Trends in drug poisoning deaths by sex, in Ireland, 2004 to 2017. European expert group on: Gender and Drugs. [online] 15 Oct 2021

- **Lynn E**, Cousins G, Lyons S, Bennett K.E. Comparing characteristics of suicide to non-suicide drug poisoning deaths, by sex, in Ireland. SSA PhD symposium side event of the SSA conference: Comparing characteristics of

suicide to non-suicide drug poisoning deaths, by sex, in Ireland. [online] 3 Nov 2021

Poster presentation

- **Lynn E,** Doyle A, Keane M, Cousins G, Bennett K.E. Drug poisoning deaths among women: a scoping review. Lisbon 23 Oct 2019; Lisbon Addiction conference

Chapter 1: Introduction

This thesis focuses on drug poisoning deaths among women, with particular emphasis on differences between women and men in potential factors associated with, and drugs involved in: all drug poisoning deaths, drug poisoning deaths involving a specific emerging drug (pregabalin), and suicide drug poisoning deaths. This chapter provides a brief background on women and drug poisoning deaths, including the wider context of drug use among women. In addition, this chapter includes a description of biological sex differences which affect drug actions, information on representation of women in clinical drug trials, and why public health research data should be stratified by sex. This chapter also presents the rationale behind the aims and objectives of the thesis, and an overview of the individual chapters within this thesis.

The principles of a public health approach, proposed by the Centers for Disease Control and Prevention, were used to guide the development of this thesis (Figure 1.1 [Centers for Disease Control and Prevention, 2022]). Specifically, this body of work addresses the first two steps of the public health approach, namely quantifying the burden of the problem of drug poisoning deaths among women (Chapters 1 and 2) and identifying risk and protective factors associated with drug-poisoning deaths in women (Chapters 2, 3, 4, 5). This work has the potential to inform future steps, seeking to develop interventions with the aim of preventing and reducing future drug poisoning deaths in women. As discussed in Chapter 6, the findings from this thesis regarding the burden of the problem and associated risk factors have been disseminated widely (Chapter 6) with recommendations for effective actions to help prevent drug poisoning deaths.

In Ireland, the National Drug-Related Deaths Index (NDRDI) publishes aggregated data on drug-related mortality, which includes drug poisonings; however, more in-depth analysis of this data could provide information on factors that specifically influence mortality among women in Ireland. The NDRDI is described in more detail below in section 1.7.1. In-depth analysis on drug poisoning deaths, stratified by sex can contribute to national policy on decreasing drug-related mortality as well as contributing to the knowledge gap that has been acknowledged internationally in this area.

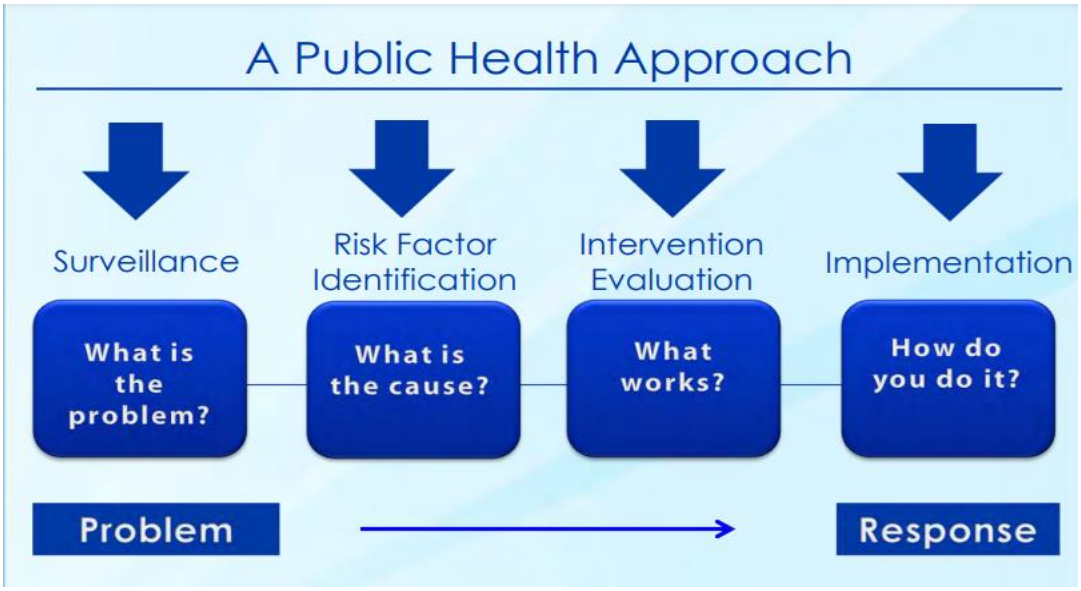


Figure 1.1 A Public Health Approach. Source: Centers for Disease Control and Prevention (CDC) [retrieved from https://www.cdc.gov/training/publichealth101/documents/introduction-to-public-health.pdf]

1.1 Women and drug poisoning deaths

A recent World Drug Report by the United Nations Office on Drugs and Crime (UNODC) estimated that 275 million people worldwide use drugs (UNODC, 2021). According to the International Narcotics Control Board (INCB), one third of the people who use drugs globally are women and drug-related harms to women, which include mortality, are often greatly under-studied with gender-disaggregated data on drug use rarely collected (International Narcotics Control Board, 2017).

Of the estimated 275 million people worldwide who use drugs, over 36 million have substance use disorder (SUD) which requires drug treatment services (UNODC, 2021). Although SUD is more commonly observed among men, evidence indicates that prevalence and patterns of types of problem drugs differ between men and women (UNODC, 2021). For example, while use of cannabis, cocaine and amphetamines is more prevalent among men, rates of non-medical use of opioids and tranquillisers are often comparable between men and women, or even more prevalent among women (Clark et al., 2015; UNODC, 2021).

Drug poisoning deaths are a leading cause of mortality among people who use drugs, and a leading cause of preventable deaths in the general population

worldwide, with rates increasing globally (EMCDDA, 2020; Shiels et al., 2020). While drug poisoning deaths are more commonly observed among men, lower prevalence of problem drug use, and drug-related mortality among women in the general population often means that women who use drugs and/or die from drug poisoning may be excluded from or insufficiently represented in research (Chapter 2). When women are included in research, lack of stratification by sex in data analysis may mask important differences, including sex specific risk factors (Masters et al., 2017). In addition, given that data on drug poisoning deaths is predominantly on men, failure to prioritise and stratify data by sex, potentially limits the generalisability of research findings to the overall population (Phillips, 2008).

Being in receipt of opioid agonist treatment (OAT) has been well established as a protective factor against all causes of mortality among people who use drugs, including drug poisoning deaths (Santo et al., 2021; Rogeberg et al., 2021; Bukten et al., 2019). A systematic review and meta-analysis on all cause and specific causes of mortality among people with opioid dependency, which included 15 randomised clinical trials and 36 primary cohort studies globally, reported OAT was associated with lower rates of mortality, especially for unintentional drug poisoning deaths (Santo et al., 2021). This protective effect of OAT appeared to be consistent across both men and women (Santo et al., 2021). Two qualitative studies examined issues around women who used drugs and access to treatment services in Dublin, Ireland (Morton et al., 2020; Ivers et al., 2021). One included a briefing paper which comprised of themes extracted from a review of existing literature, and feedback from practitioners and key agency representatives to explore issues and challenges surrounding access to homeless, addiction, and health services for women (Morton et al., 2020). The other qualitative study included in-depth qualitative interviews with 22 women attending drug treatment services, 22 key stakeholders who directly or indirectly provided services (including managers and frontline staff from addiction services, and representatives from family services, domestic violence services, suicide prevention services, and State agencies), 28 participants attending a live online community consultation, and 25 individuals contributing to an online submission forum (Ivers et al., 2021). Findings from these two studies show that despite the potential benefits associated with OAT, women expressed reluctance to engage with services because of perceived barriers to services due to the complex needs of women who use drugs. These barriers include stigma, fear, and shame, in

addition to being afraid of losing their children, lack of childcare facilities and past negative experiences with service providers (Ivers et al., 2021; Morton et al., 2020). In addition, there is very little self-referral for treatment among women and late referral to specialised treatment services by general practitioners (Ivers et al., 2021; Morton et al., 2020). These perceived barriers to assessing treatment and late referrals to specialised treatment for women suggest treatment services are failing to reach a vulnerable cohort of people who use drugs. Enhanced understanding of female-specific risk factors related to drug poisoning deaths may contribute to the evidence-base on which to integrate a sex-specific dimension to drug policies and practices, including treatment provision, to reduce not only drug poisoning deaths but overall drug-related harms among women (Clark et al., 2015), (Chapter 2).

Suicide is a significant public health concern with over 700,000 people worldwide dying by suicide each year (WHO, 2021a). A matched cohort study examining mortality in people who use illicit opioids in England reported the rate of suicide deaths was 16 times the expected rate among women who use illicit opioids when compared to women in the general population; however, for men who use illicit opioids the rate of suicide deaths was five times the expected rate (Lewer et al., 2021). Results from a Scottish mixed-methods study and an observational study in the United States show that suicide drug poisoning deaths account for a greater percentage of drug-related deaths among women than men (Tweed, 2020; Szymanski et al., 2016). Drug poisoning deaths are a potentially preventable method of suicide. More focus should be given to prevention measures in medical management, including better detection of drugs used with appropriate treatment intervention, appropriate prescribing of psychiatric drugs, enhanced information to users and family members about the dangers of drugs, and controlling availability of drugs (Värnik et al., 2011); however, there is a lack of research on this topic, including the specific drug groups involved in these deaths (Miller et al., 2020).

Dual diagnosis of substance use disorder with other mental health conditions, is very common (European Monitoring Centre for Drugs and Drug Addiction, 2021a) and therefore, psychotropic drugs may be co-prescribed with OAT medications. In Ireland the main drug prescribed for OAT is methadone (Durand et al., 2020). The importance of pharmacodynamic and pharmacokinetic differences between men and women have not always been forefront in the design of clinical drug trials, some of which may involve these drugs (Graziani & Nisticò, 2015). When examining specific

drugs involved in drug poisoning deaths, biological differences between men and women are not generally taken into consideration.

1.2 Biological differences between men and women

The importance of biological differences between men and women in relation to drug pharmacokinetics and pharmacodynamics is now well recognised. Pharmacokinetics in women relative to men can vary according to several factors including; lower lean body mass among women, resulting in lower base metabolic rate; sex differences in intestinal activity with slower gastrointestinal motility and intestinal enzyme activity in women relative to men, which can affect absorption of drugs and may require women to have a longer interval between eating and taking medications that need to be absorbed on an empty stomach; sex differences in kidney enzymes and slower renal clearance in women of some drugs, such as pregabalin, which may require a dosage adjustment for women (Whitley and Lindsey, 2009; Ibarra et al., 2017) and differences between the sexes in circulating levels of endogenous hormones, such as testosterone and estradiol (Miller, 2001).

Pharmacodynamic differences between sexes include women being more sensitive to and experiencing enhanced effects of alcohol and certain other drugs including opioids, selective serotonin reuptake inhibitors and antipsychotics (Algren et al., 2013; Whitley and Lindsey, 2009). Women have an increased risk of torsades de pointes, a potentially fatal arrhythmia, after taking drugs which prolong the QT interval (Makkar et al., 1993). In addition to cardiac drugs, drugs such as methadone and psychotropic drugs, which are frequently implicated in drug poisoning deaths, are known to be associated with QT interval prolongation (Makkar et al., 1993; Ito et al., 2004). The risk of developing torsades de pointes may not be linked to high dosage of drugs such as methadone but may increase with the use of multiple drugs which prolong the QT interval (Vieweg et al., 2013).

Historically women have been underrepresented in clinical drug trials, therefore specific adverse reactions among women in relation to ‘old’ medications, such as methadone and diazepam, which are commonly implicated in drug poisoning deaths in Ireland (Chapter 3), may be unknown.

1.3 Representation of women in clinical drug trials

Historically, clinical drug trial participants have predominantly involved men, especially for phase I clinical trials investigating tolerability, clinical pharmacology, dose-related side effects and early evidence of efficacy (Fisher & Kalbaugh, 2011). The historic underrepresentation of women in clinical trials was influenced by the historic assumption that the male perspective represented the norm (Criado-Perez, 2019). However, it has become increasingly apparent that the male response to drugs is not generalisable to women. Preclinical trials have also historically excluded female animals as a means of controlling for hormonal variation (Zucker & Beery, 2010). However, as highlighted by Johnson et al. (2009), it is essential to include examination of hormonal variations to understand their influence on drugs being researched (Johnson et al., 2009). In addition, the bias against women in clinical trials stems in part from a 1977 decision by the Food and Drug Administration (FDA) in the United States, that prevented women of reproductive age from participating in phase I and early phase II studies unless the trials related to life-threatening illnesses (Miller, 2001; Liu & Mager, 2016). The thalidomide tragedy in Europe influenced this decision (Ravindran et al., 2020). However, concerns raised on the general underrepresentation of women in drug trials resulted in the FDA reversing the ban in 1993 (Liu & Mager, 2016).

Rather than protecting women, evidence shows their exclusion from trials has led to an unrepresentative assessment of drug efficacy and side effects, potentially leaving women at risk of serious harm (Carey et al., 2017). In fact, it has been reported that women are 50 to 70 percent more likely than men to experience an adverse drug reaction (Whitley and Lindsey, 2009). A report from the United States found that, of the ten drugs removed from the market in the United States between 1997 and 2000, eight were withdrawn because of side effects that occurred only, or mainly, in women (Nowogrodzki, 2017).

While representation of women in clinical trials has improved, more work is required in this area. A 2011 review examining 86 studies from nine high impact journals showed that two-thirds of the trials did not report results by sex (Geller et al., 2011). A cross-sectional study published in 2018, looking at 38 drug trials involving frequently prescribed drugs approved for use between 1986 and 2015, where data was publicly available, concluded that, overall, women are studied in adequate

proportions with 47% of participants identified as women. However, only 22% of participants in phase I clinical trials were women and the number of women in more than 25% of trials did not match the proportion of women affected by the diseases being studied (Labots et al., 2018). While more equal representation of women in new clinical drug trials is more likely, some well-established drugs frequently used in the treatment of public health issues, including SUD, did not include women participants in their clinical trials. For example, the effects of diazepam, the main benzodiazepine implicated in all drug poisoning deaths in Ireland (Health Research Board, 2019; Chapter 3), and the main benzodiazepine type drug dispensed through the Irish Health Service Executive (HSE) Primary Care Reimbursement Service (PCRS), with a higher number of items dispensed to women relative to men (HSE, personal communications), was never tested in randomised clinical trials with women participants (Schiebinger, 2003).

Underrepresentation of women in clinical trials and in health research may fail to identify differences in responses to drug therapies between men and women, and also inhibits appropriate guidance for prescribing of drugs in these groups (Nowogrodzki, 2017).

1.4 Why public health data should be stratified by sex

A key element to improving the lives of women and girls worldwide is to address sex and gender inequalities, as highlighted in the United Nation's Global Agenda for Sustainable Development (United Nations, 2021). One strategy towards gender equality is gender mainstreaming, defined as "the integration of a gender perspective into the preparation, design, implementation, monitoring and evaluation of policies, regulatory measures and spending programmes, with a view to promoting equality between women and men, and combating discrimination" (European Institute for Gender Equality, What is gender mainstreaming? [accessed 23 Oct], 2021).

The datasets used in this thesis use the biological sex categories of male/female in data stratification, rather than gender identity. While gender fundamentally refers to social and cultural influences and how individuals perceive themselves in relation to social or cultural norms, and sex refers to the biological

makeup of a person, both definitions are often blended in health research (Caughey et al., 2021; Johnson et al., 2009; Miller, 2001).

As stated by WHO, research is fundamental to informing both policy development and service delivery (WHO, 2021b). It is essential to include sex and gender in public health research to bridge the gap in public health knowledge and to advance gender and sex equality. However, sex and gender are in general, poorly considered in public health research (VanHagen et al, 2021; Johnson et al., 2009). A study by the Council of Europe's Pompidou Group investigating women's use of prescription drugs for non-medical reasons, reported that understanding the gender dimension of drug use and drug use disorders is a critical requirement in developing effective policy and practice to help prevent mortality associated with drug use (Clark et al., 2015). Failure to stratify results by sex is a missed opportunity to provide evidence on differences or similarities among men and women.

1.5 Rationale for the thesis

Reports that drug-related deaths in women, which include direct drug poisoning deaths and deaths due to medical or traumatic causes among people who use drugs, are growing at a faster rate than in men is concerning (UNODC, 2021; Tweed, 2020; VanHouten et al., 2019; Public Health England, 2016). While the majority of people who use drugs are men, the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) reported that women who use drugs are more likely to develop adverse health effects and social exclusion than their male counterparts (European Monitoring Centre for Drugs and Drug Addiction, 2021b).

Results from a large cohort study examining the causes of death among people who use illicit opioids in England reported that while crude mortality rates were higher among men, women who used drugs had a higher standardised mortality rate relative to women in the general population, with drug poisoning deaths the main cause of death among this study cohort (Lewer et al., 2021). As previously highlighted, the same study reported the observed rate of suicide among people who used illicit opioids was higher than the expected rate for women than for men when compared to the general population (Lewer et al., 2021). Despite drug poisoning deaths accounting for a larger proportion of suicide deaths among women relative to men (Petrosky et al., 2020; Värnik et al., 2008), the majority of drug poisoning deaths

in the general population, including drug poisoning deaths involving opioids, are unintentional and potentially preventable (Olfson et al., 2019; Austin et al., 2017). A systematic review and meta-analysis on all cause and cause specific mortality among people using extramedical opioids, which included 124 studies, reported drug poisoning deaths as the main cause of death among this cohort (Larney et al., 2020). This further highlights the need to examine drug poisoning deaths by sex in more detail to provide evidence to influence policy and practice to decrease these deaths.

The EMDCCA definition for drug poisoning deaths focuses on deaths directly related to the consumption of opioid drugs and/or illicit substances on their own or in combination with licit drugs (EMCDDA, 2007), with the majority of these deaths involving opioids (EMCDDA, 2021c). The EMCDDA definition for a drug poisoning death is comparable across all EU countries, Norway, and Turkey. Using the EMCDDA inclusion criteria for a drug poisoning death, northern European countries such as Sweden and Norway have, in the most recent years of available data, reported a similar profile to Ireland in relation to drug induced mortality rates (EMCDDA, 2021c). However, while NDRDI data includes deaths covered by the EMCDDA definition, it has a wider inclusion criterion. The NDRDI includes data on drug poisoning deaths in the general population which involve alcohol and/or licit drugs and/or illicit drugs. For this reason, the annual number of drug poisoning deaths in Ireland, published by the NDRDI, are higher than drug poisoning deaths reported to the EMCDDA, albeit the trend in drug poisoning deaths is similar using each definition (Figure 1.2). The latest data published by the NDRDI shows that prescribable drugs are the main drugs involved in drug poisoning deaths in Ireland with prescribable drugs implicated in 67% of poisoning deaths in 2017 (Health Research Board, 2019). This highlights the need to examine drug poisoning deaths involving prescribable drugs in more detail.

The most recent Irish National Drug and Alcohol Survey, for the first time, included questions on non-medical use of sedatives/tranquillisers, with a similar proportion of males (0.6%) and females (0.4%) reporting non-medical use of sedatives/tranquillisers in the last year (Mongan et al, 2021). In addition, women were more likely than men to report recent use of opioid pain relievers and women aged 15-34 years most likely to reporting non-medical use of opioid pain relievers in the last year (Mongan et al. 2021). This survey also shows an increase in the number of both men and women using illegal stimulants, especially cocaine (Mongan

et al., 2021). Of interest, results from the latest European school survey project on alcohol and drugs reported higher prevalence rates among girls than boy for non-medical use of sedatives/tranquillisers (ESPAD, 2020). This shows that drug use continues to be an issue in society.

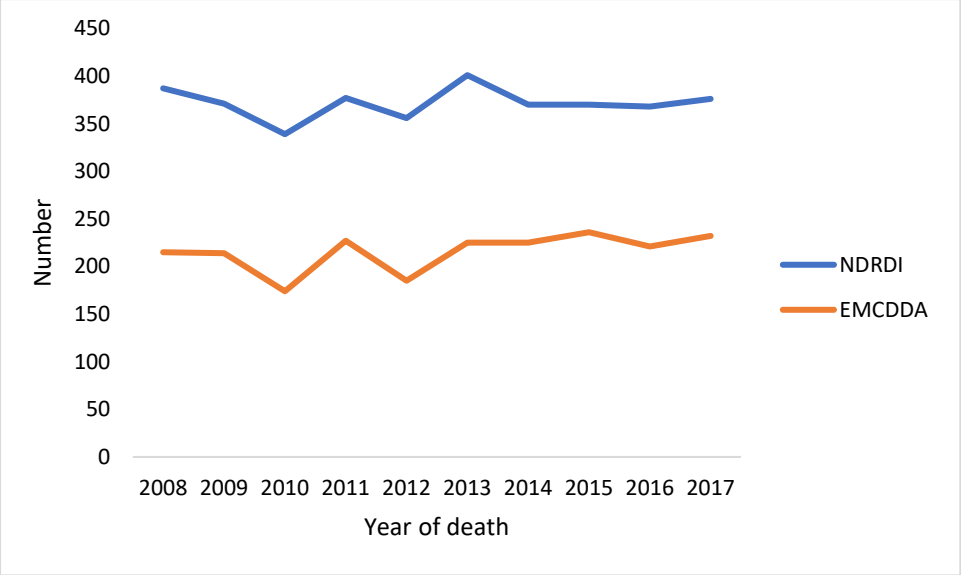


Figure 1.2 Trends in drug poisoning deaths in Ireland using the EMCDDA and the NDRDI inclusion criteria, 2008 to 2017

Knowledge on the specific drugs involved in deaths, recorded by the NDRDI, with data stratified by sex, can assist in providing evidence, and raise awareness among service users, service providers, and policy makers to implement appropriate interventions. Interventions may need to be drug and sex specific to help prevent these unnecessary deaths. It is also important to examine factors associated with emerging new drugs, including licit drugs, implicated in drug poisoning deaths. This will assist in gaining insight into how to curb their involvement in drug poisoning deaths and to inform policy on helping to prevent such deaths.

In Norway, a recent study examining autopsy findings on drug poisoning deaths reported that deaths involving only prescription drugs were more common in women (Edvardsen & Clausen, 2022). In Ireland, an increase in drug poisoning deaths involving pregabalin, a prescription drug, has been reported since 2012 (HRB, 2019) and this corresponds to reports from other European countries (European Monitoring Centre for Drugs and Drug Addiction, 2021c). However, there is a lack of data on sex-specific factors related to these deaths. The INCB reported

that limited data is available on overdose mortality due to prescription drug abuse (International Narcotics Control Board, 2017).

Men account for most of all drug poisoning deaths; however, drug poisoning deaths account for a smaller percentage of suicides among men relative to women (Petrosky et al., 2020; Värnik et al., 2008). Data from the NDRDI shows that, relative to men, a higher proportion of drug poisoning deaths among women were suicide deaths (Figure 1.2). It is important to examine the extent to which individual and social contextual factors, as well as specific drugs/drug groups influence the risk of a drug poisoning being a suicide death and to determine if there are any differences between men and women.

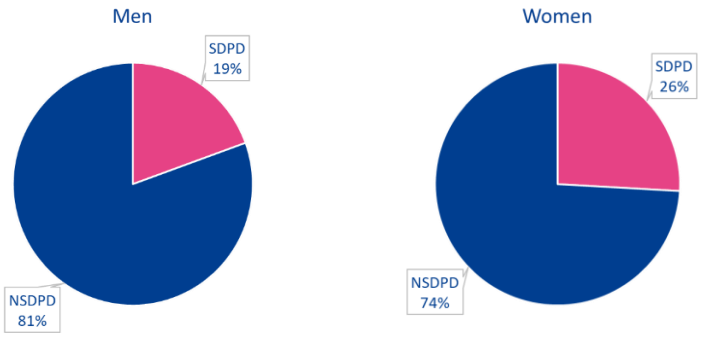
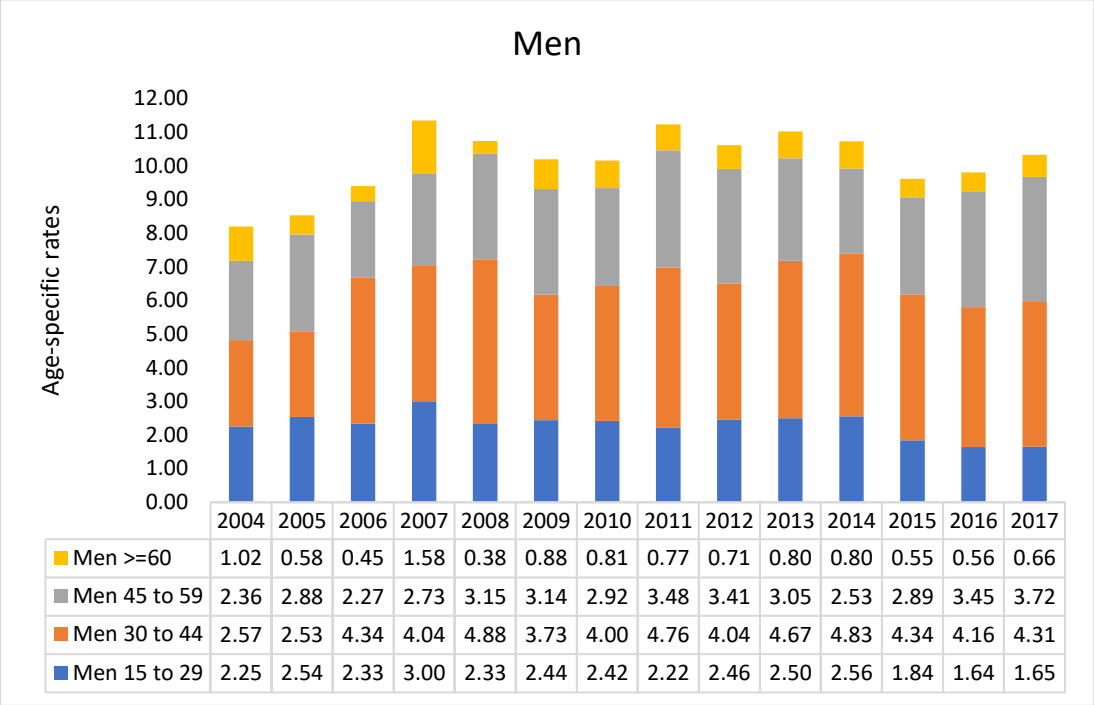


Figure 1.3 Suicide and non-suicide drug poisoning deaths, by sex, (2015-2017 combined), n = 1114

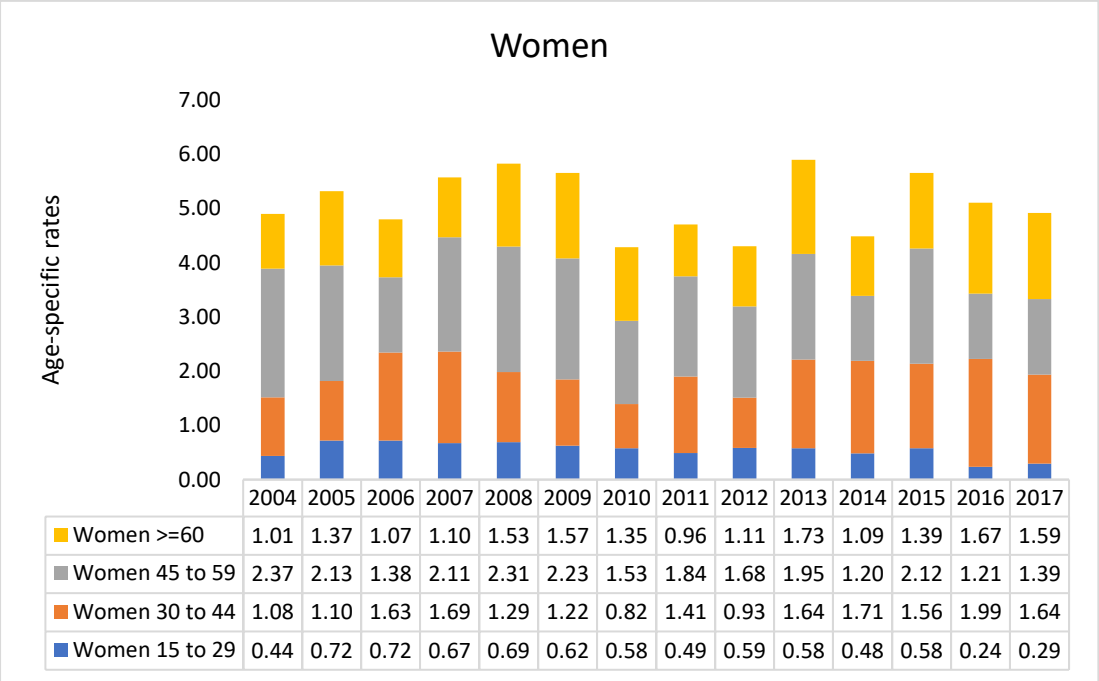
For both men and women, NDRDI data from 2004 to 2017 shows a decline in the age-specific crude rate of drug poisoning deaths among young people aged 15 to 29 years and an increase in the rate of drug poisoning deaths among those aged 30 to 44 years, albeit more substantial among men. A decrease in the rate of drug poisoning deaths in the age group 45 to 59 years of age was observed over the study period among women, but for men an increase was observed in the rate of drug poisoning deaths among this age group. The opposite is observed in the oldest age group (65 years of age or older) with an increase in the rate of drug poisoning deaths observed among women, but a decrease observed among men (Figures 1.2 & 1.3). Given that age distribution in the population can change from year to year, age-standardised rates give an accurate indication of overall annual trend changes over time as they account for progressive changes in age structure of a population.

Chapter 3 includes age-standardised rates of drug poisoning deaths in trend analyses.



	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017
Men >=60	1.02	0.58	0.45	1.58	0.38	0.88	0.81	0.77	0.71	0.80	0.80	0.55	0.56	0.66
Men 45 to 59	2.36	2.88	2.27	2.73	3.15	3.14	2.92	3.48	3.41	3.05	2.53	2.89	3.45	3.72
Men 30 to 44	2.57	2.53	4.34	4.04	4.88	3.73	4.00	4.76	4.04	4.67	4.83	4.34	4.16	4.31
Men 15 to 29	2.25	2.54	2.33	3.00	2.33	2.44	2.42	2.22	2.46	2.50	2.56	1.84	1.64	1.65

Figure 1.4 Age-specific rates of drug poisoning deaths among men, NDRDI 2004 to 2017



	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017
Women >=60	1.01	1.37	1.07	1.10	1.53	1.57	1.35	0.96	1.11	1.73	1.09	1.39	1.67	1.59
Women 45 to 59	2.37	2.13	1.38	2.11	2.31	2.23	1.53	1.84	1.68	1.95	1.20	2.12	1.21	1.39
Women 30 to 44	1.08	1.10	1.63	1.69	1.29	1.22	0.82	1.41	0.93	1.64	1.71	1.56	1.99	1.64
Women 15 to 29	0.44	0.72	0.72	0.67	0.69	0.62	0.58	0.49	0.59	0.58	0.48	0.58	0.24	0.29

Figure 1.4 Age-specific rates of drug poisoning deaths among women, NDRDI 2004 to 2017

Previously, the National Family Support Network (NFSN) in Ireland has called for more family-focused research on drug-related mortality (Lynn, 2017). The NFSN, which has now ceased operations, was an autonomous self-help organisation that provided support to families and respected the experiences of families affected by substance misuse in a welcoming, non-judgemental atmosphere. According to the NFSN, the mother in a family is often the main carer for children, and more detailed research into deaths among women due to drug misuse would enrich the knowledge in this area and contribute to reducing this knowledge gap highlighted by families affected (Lynn, 2017).

There is a need for research to identify sex-specific factors, drugs and intent associated with drug poisoning deaths to inform new policies, and to achieve the overall goal of deceasing premature drug poisoning deaths among both men and women. Findings from this thesis should provide more evidence to inform policy and practice in this regard.

1.6 Thesis aims and objectives

The overarching aim of this research is to explore what is already known about poisoning deaths among women, identify areas requiring additional knowledge and provide evidence to inform the knowledge base in this area. In identifying the evidence, the aim is to inform policy and practice to help prevent premature deaths among women due to drug poisonings. The specific objectives of the study are:

I. To investigate the extent of existing knowledge on drug poisoning deaths among women.

II. To explore trends in drug poisoning deaths in Ireland stratified by sex and identify specific drugs/drug groups involved in drug poisoning deaths among women and examine whether they differ from drug poisoning deaths among men.

III. To explore potential factors associated with drug poisoning deaths involving pregabalin, an emerging drug in drug poisoning deaths.

IV. To explore potential factors associated with suicide drug poisoning deaths relative to non-suicide drug poisoning deaths, stratified by sex.

1.7 Data sources

Data was extracted from two large national databases, the National Drug-Related Deaths Index (NDRDI) and the Irish Health Service Executive (HSE) Primary Care Reimbursement Services (PCRS).

1.7.1 The National Drug-Related Deaths Index (NDRDI)

The National Drug-Related Deaths Index (NDRDI) is the national census on drug and alcohol-related deaths and indirect deaths among people with a lifetime history of using drugs and/or were alcohol dependent, in Ireland. Following extensive consultation and discussion, the National Drug Strategy Team agreed that the general mortality register was not a sufficient basis on which to identify drug-related deaths or deaths among people who used drugs. This led to the establishment in 2005 of a specific index, the NDRDI, in order to comply with Action 67 of *'Building on Experience: National Drug Strategy 2001-2008'* (Department of Tourism, Sport and Recreation, 2001). That action called for the development of a system for recording drug-related deaths and deaths among people who use drugs to enable the State and associated agencies to respond in a timely manner, with accurate data. The objectives of the NDRDI also include identifying and prioritising areas for intervention and prevention and measuring the effects of such interventions. The remit of the NDRDI was further expanded in January 2006 to include alcohol-related deaths and deaths of people with alcohol dependency. The NDRDI does not collect data on drug poisoning deaths due to the toxic effect of drugs which were prescribed to the individual and consumed as directed by their medical practitioner.

The NDRDI is maintained by the National Health Information Systems (NHIS) Unit of the Health Research Board (HRB). The NDRDI is jointly funded by the Department of Health and the Department of Justice. The NDRDI has a steering committee, co-chaired by the Department of Health and the Department of Justice, which includes among others, representatives of families affected by drug-related deaths, representatives from the Irish Coronial Service, an Garda Síochána, the

State Laboratory, the Office of the State Pathologist and relevant Health Service Executive areas.

To ensure a complete and accurate Index, the NDRDI records data from four sources: the Coroner Service, the Hospital In-Patient Enquiry (HIPE) scheme, the Central Treatment List (CTL), and the General Mortality Register (GMR)/ Central Statistics Office (CSO). The data is collected retrospectively on an annual basis.

There is no national coronial database in Ireland; therefore, NDRDI coronial data collection involves annual visits to each of the coronial districts in Ireland (currently there are 36 coronial districts in Ireland), manually reviewing all files pertaining to deaths reported to the coroners and extracting relevant data to be entered onto a secure online data collection tool onsite. NDRDI research staff, of whom I am a member, undertake an annual census of all closed coronial files. In Ireland, a coroner has responsibility under the law to investigate the circumstances of all sudden, unexplained, violent, and unnatural deaths in order to establish the 'who, when, where and how' of the death. If a death is not immediately explicable, the coroner may order an autopsy to help establish the cause of death. Following an autopsy, a coroner may proceed to an inquest to establish the identity of the deceased, how, when, where the death occurred and return a verdict. Depending on the type of death investigation, the coronial file can contain extensive information, including autopsy and toxicology reports, depositions from family members, friends, witnesses, and medical personnel. In addition to police reports and medical records where relevant. The inquest procedure can be a lengthy process and may not be concluded for a considerable period of time, therefore real time data is not achievable. Currently inquests can take up to 24 months from the date of death to be heard (Dublin Districts Coroner's Court, 2022). Data from the remaining three sources is submitted electronically to the NDRDI on an annual basis.

The Healthcare Pricing Office (HPO) of the Health Service Executive (HSE) manages the HIPE scheme in Ireland. The HIPE scheme is a health information system designed to collect clinical and administrative data on discharges from, and deaths in acute public hospitals across Ireland. Information is only recorded for people who are admitted as inpatients, therefore people who attend Accident and Emergency Units for treatment but die in Accident and Emergency Units prior to being admitted as inpatients, are not included in HIPE. Data from HIPE is used by

policymakers, clinical teams, and researchers. Clinical data is coded using the 8th Edition of the International Statistical Classification of Diseases and Related Health Problems (World Health Assembly, 1966). An automated programme was developed by the HIPE department of the HPO in collaboration with NDRDI staff. This system facilitated an annual electronic download of data on deaths which meet the NDRDI inclusion criteria. Data received from the HIPE scheme includes demographics and up to thirty diagnoses.

The Central Treatment List (CTL) is a national administrative database, established in 1998 under Statutory Instrument No 225 of the Misuse of Drugs (Supervision of Prescription and Supply of Methadone) Regulations (Government of Ireland, 1998), to regulates the dispensing of methadone for opioid substitution treatment. These regulations were replaced in 2017 by the Statutory Instrument No 522, to allow for the inclusion of buprenorphine medicinal products authorised for opioid substitution treatment (Government of Ireland, 2017). The CTL records demographic and clinical data on people in receipt of opioid agonist treatment, including methadone or buprenorphine, in Ireland. An electronic download of data on deaths among people registered on the CTL is received by the NDRDI on an annual basis. Data received includes demographics, data pertaining to treatment including type of treatment provided, and date of death.

Every birth, death, and marriage occurring in Ireland must be registered with the General Register Office (GRO). The data on these registration forms is then forwarded to the Vital Statistics section of the Central Statistics Office (CSO) for the production of statistics. The CSO categorises the cause of each death using the WHO diagnostic coding manual on the international classification of diseases (known as ICD categories). The tenth revision of this manual is currently used by the CSO. The CSO provide an annual electronic download of demographics and cause of death of all registered deaths that meet the inclusion criteria for the NDRDI. In addition, the cause of death for data received from other data sources for the NDRDI can be verified through the General Deaths Register in the CSO. Data received from the CSO includes demographics, occupation, employment status and cause of death.

Cases from the different data sources are cross-matched on a selection of variables, including name, gender, county of residence, date of birth and date of

death. This allows the NDRDI to eliminate duplicates and maximise the amount of information available on each case recorded on the database.

For deaths which occurred in 2015 onwards, the National Office for Suicide Prevention (NOSP) have requested the Health Research Board to expand the NDRDI data collection from coronial files to include all deaths with a verdict of suicide or a record of suicide based on the balance of probability that the deceased took their own life. This broader definition of suicide is based on the Rosenberg et al.,(1988) operational criteria for the determination of suicide. The process undertaken to include deaths based on the balance of probability was validated by a team, which included a national expert and an international expert in the area of suicide. In addition, a number of deaths included based on the balance of probability were reviewed by an expert review group to confirm that they met the inclusion criteria. Inclusion of the broader definition of suicide, allows, for the first time in Ireland, more robust analysis on suicide drug poisoning deaths. This analysis would contribute to a greater understanding of these deaths, with particular reference to quantifying the impact of known risk behaviours including the impact of drugs, by sex.

NDRDI data is used nationally to define the extent of drug and alcohol-related deaths, to inform policy and to assess the effectiveness of responses aimed at preventing deaths from drugs or alcohol. It complies with the reporting requirements for the EMCDDA and as such is used to meet Ireland’s mandatory reporting requirements to the EU, UN and WHO. Drug-related deaths and deaths among people who use drugs is one of the EMCDDA's key indicators to measure the consequences of the drug situation. The protocol for the data collection, validation and analysis of the data required by the EMCDDA is the '*EMCDDA Scientific Report: The DRD Standard Version3 (2002)'.* This was developed and validated by European experts. Data required by the EMCDDA pertains to illicit drugs on their own or in combination with licit drugs. However, NDRDI data is more extensive and includes data on drug poisoning deaths in the general population which involve alcohol and/or licit drugs with or without illicit drugs. The NDRDI does not include drug poisoning deaths among people where the drug was consumed as directed under medical supervision.

The Department of Health categorises the establishment of the NDRDI as research in the interest of the public good for a number of reasons. The previous

lack of accurate knowledge on drug and alcohol-related deaths and deaths among substance users in Ireland and the necessity for such knowledge to inform health policy, planning and evaluation. In addition, the families of people who use drugs (through the National Family Support Network) advocated that the government develop a mechanism to measure the burden of premature deaths among drug users since 1999.

Data is usually reported annually however due to public health Covid-19 restrictions data collection from coronial sites has been delayed. Therefore, for the purpose of studies included in this thesis, the most complete years of data available includes up to and inclusive of 2017 deaths.

There are two broad categories of deaths reported by the NDRDI:
Poisonings: a death within the general population directly attributable to the consumption of one or more substance(s) and may be intentional or unintentional.
Non-poisonings: a death due to either a medical or traumatic cause among those who used drugs and/or were alcohol dependent.

NDRDI data used in this thesis pertains to the category of deaths that meet the inclusion criteria for drug poisoning deaths.

1.7.2 The Health Service Executive (HSE) Primary Care Reimbursement Services (PCRS)

The Health Service Executive (HSE) Primary Care Reimbursement Scheme (PCRS) register includes data on medicines dispensed to citizens with full eligibility for the General Medical Services (GMS) scheme. 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. However, the HSE PCRS-GMS pharmacy claims database funds the majority of pharmaceutical expenditure and represents the single largest pharmacy claims dataset in Ireland (Sinnott et al., 2017). 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. 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. As of 2015, almost 40% of the Irish population were covered by the GMS scheme (Sinnott et al., 2017).

The latest published data from the NDRDI (Health Research Board, 2019) shows the percentage of women who died as a result of drug poisonings has stabilized, but more in-depth analysis looking at what drugs were involved in these deaths, and if there is any evidence of change in drug habits would give more insight into how policy can help decrease these deaths.

1.8 Method

This research involved four separate, but related studies designed to address the study objectives. The first study was a scoping review exploring the topic of drug poisoning deaths among women. Scoping reviews provide the opportunity to undertake a broad overview in relation to specific topics. Scoping reviews differ to the more orthodox systematic review, which tend to be used to address very specific research questions and/or assess the quality of information available on a discretely defined topic (Arksey and O'Malley, 2005); (Tricco et al., 2016); (Peters et al., 2015). According to Peters et al (2015), a scoping review is a valid method of knowledge syntheses to explore areas that have not been comprehensively reviewed. As scoping reviews are used to gain a greater understanding of existing knowledge, identify gaps in knowledge and provide recommendations for future research, practices and policy (Peters et al., 2015); (Tricco et al., 2016), a scoping review was undertaken to explore the extent, range and nature of evidence in relation to drug poisoning deaths among women.

The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist (STROBE Statement, 2007), was used as a guide to structure the remaining three studies.

Data from the National Drug-Related Deaths Index (NDRDI) and the PCRS-GMR were analysed to establish trends in drug poisoning deaths and prescription drug dispensing data, and specific factors associated with pregabalin positive poisoning deaths, an emerging drug involved in drug poisoning deaths in Ireland. NDRDI data was also used to compare characteristics of suicide to non-suicide drug poisonings by sex.

Joinpoint Regression Program version 4.8.0.1 was used to examine trends in drug poisoning deaths over a 14-year period. Joinpoint regression is a statistical software package that enables the user to test whether or not an apparent change in

trend is statistically significant. Joinpoint regression identifies if there is an overall trend change and if there are any statistically significant reference periods within the overall study time period where there was a significant trend change.

The remaining two studies examined factors associated with the study outcomes using logistic regression models. Interactions were assessed between sex and other covariates included in adjusted models to clarify that stratification by sex was appropriate. Adjusted logistic regression models included all factors found to be significant at $p<0.10$ in the unadjusted analyses. Prior to inclusion in the adjusted logistic regression models, correlations between covariates were calculated to assess for any collinearity. Due to a strong collinearity between various drugs/drug groups and other covariates, separate unadjusted logistic regression models were computed for drugs involved in these deaths. Odds ratios (OR) and 95% confidence intervals (CI) were reported for both the unadjusted and adjusted models. Findings are presented overall and by sex.

1.9 Thesis outline

This thesis involves four papers that address the research questions previously outlined. All of these papers have been published in high impact journals. Each chapter is preceded by a foreword that details the status of the paper, the study aim(s), and the contribution of each author.

Chapter 2 presents a scoping review of drug poisoning deaths among women. The findings show that most data available on drug poisoning deaths among women involved epidemiological trends with limited in-depth analysis of factors explaining these trends. The dearth of knowledge in the area of drug poisoning deaths among women gives impetus to the need to explore the contribution of candidate factors or a combination of these factors to drug poisoning deaths among women. This paper was published in the *Journal of Studies on Alcohol and Drugs*.

Chapter 3 presents trend analysis in age standardised mortality rates (ASMR) for drug poisoning deaths in Ireland, over a fourteen-year period, 2004 to 2017. Joinpoint Regression Program version 4.8.0.1 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. The relationship between death and prescription rates for benzodiazepines and antidepressants is also assessed. This paper was published in the *BMJ Open.*

Chapter 4 extends on findings from chapter 3. Pregabalin is one of the drugs influencing the more recent increase in drug poisoning deaths involving two or more CNS depressant drugs. This paper examines factors associated with all drug poisoning deaths from 2013 to 2016 where pregabalin was present on toxicology, with results stratified by sex. This paper was published in *Drug and Alcohol Dependence*.

Chapter 5 presents findings on comparing characteristics of suicide to non-suicide drug poisonings, by sex. This study included, for the first time in Ireland, analysis of suicide drug poisoning deaths using both the narrow (legal) definition of suicide, being beyond reasonable doubt and the broader (based on the balance of probabilities) definition based on the Rosenberg criteria (Rosenberg et al., 1988). This paper was published in the *Journal of Affective Disorders* in March 2022.

Finally, Chapter 6 discusses the overall findings of this thesis, implications, and the potential impact of the findings. The strengths and limitations of this thesis and recommendations for future research are also presented.

1.10 References

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Chapter 2: Drug poisoning deaths among women: a scoping review

This chapter is based on the published paper: Lynn, E., Doyle, A., Keane, M., Bennett, K., & Cousins G. (2020). Drug poisoning deaths among women: a scoping review. *Journal of Studies on Alcohol and Drugs*. *81*(5), 543-55. https://doi:10.15288/jsad.2020.81.543

Study aim

The aim of this review is to map the extent, range, and nature of evidence in relation to drug poisoning deaths among women to inform future research, policy, and practice. In addition, this review will aim to identify gaps in knowledge for future research. An a priori study protocol was developed which pre-defines the objectives and methods. It also included agreement on a tailored data charting tool to be used (Appendix 2.1).

Author contributions

Ena Lynn (EL) developed the search strategy with the assistance of Paul Murphy, Information Specialist, RCSI library. All titles and abstracts were reviewed by EL. Anne Doyle (AD) was the second reviewer. AD reviewed all excluded titles and abstracts to ensure accuracy. Full text publications were then reviewed independently by EL and AD. Any uncertainty in relation to publication eligibility was resolved through discussion with EL, AD and MK. EL charted key data from the fully reviewed publications. EL was responsible for writing the manuscript and revised the manuscript in response to feedback from all authors. Martin Keane provided guidance on best practice for undertaking a scoping review. All authors provided critical input to drafts of the paper and approved the final manuscript.

2.1 Abstract

Objective: Drug poisoning deaths among women remain a challenge for public health policy and have increased at a higher rate relative to men. Although biological, social, and psychological differences between men and women can have an influence on drug poisoning deaths, sex is rarely considered. The objective of this study is to explore the extent, range, and nature of evidence in relation to drug poisoning deaths among women.

Methods: A scoping review was conducted according to the Arksey and O'Malley framework. A comprehensive search was performed using MEDLINE, Embase, CINAHL and Web of Science; supplemented by gray literature, including national and international reports and government documents and consultation with experts. Publications in English from June 1, 1998 to November 2, 2019 were included. Two reviewers independently screened publications for inclusion.

Results: The search identified 5,316 individual publications, and 61 met the inclusion criteria (46% from Europe; *n* = 28). The main candidate factors identified as contributing factors to drug poisoning deaths among women included age; opioid drugs, especially prescription opioids; other prescription drugs, particularly antidepressants; mental health issues; barriers to treatment; victim of violence; alcohol use; polydrug use; and history of imprisonment.

Conclusions: The majority of studies on drug poisoning deaths among women involved descriptive epidemiological data, primarily prevalence estimates, with limited in-depth analyses of factors explaining these trends. To inform policies and practices to prevent drug poisoning deaths among women, more evidence is required on risk factors specifically related to women.

2.2 Introduction

Detailed segregated data on drug-related harms by men and by women, which include drug poisoning deaths, are lacking (European Monitoring Centre for Drugs and Drug Addiction [EMCDDA], 2015; International Narcotics Control Board [INCB], 2017); U.S. Department of Health and Human Services, Office on Women's Health [USDHHS], 2017). This gap in knowledge may mask important differences between men and women in drug poisoning deaths and associated risk factors (Masters, et al., 2017).

For the purpose of this scoping review, *drug poisoning deaths* include all manners of death (among women) directly attributable to the toxic effects of drugs (other than alcohol on its own), otherwise known as "direct drug induced" or "overdose" deaths.

One third of people who misuse drugs (both licit and illicit) globally are women (INCB, 2017; United Nations Office on Drugs and Crime [UNODC], 2018). In 2016 there were 63,632 drug poisoning deaths reported in the United States, with the age-adjusted rate for drug poisoning deaths for males (26.2 per 100,000), almost double that of females (13.4) (National Center for Health Statistics, 2018). According to the EMCDDA, 8,238 drug poisoning deaths (22% women, 78% men) were reported in European Union (EU) countries in 2016 (EMCDDA, 2019). The EMCDDA (2019) suggest that because of underreporting in some EU countries, different methodologies in toxicology analysis and differences in registration processes that can lead to reporting delays, these estimates may represent an underestimate of the true prevalence; therefore, drug poisoning deaths remain a major challenge for public health policy. Although the absolute numbers are higher in men, epidemiological trends have shown that drug poisoning deaths among women have increased at a higher rate relative to men, especially in relation to intentional drug poisoning deaths (Osborn, 2018; Tyrrell et al., 2017). To develop effective policy and practice responses to drug use and associated mortality among women, it is vital that evidence is stratified by sex (Clark et al., 2015; Mazure & Fiellin, 2018) because the biological, social and psychological differences between men and women can have an impact on all aspects of drug misuse (Tuchman, 2010).

The importance of sex-specific drug policies and treatment services, and of exploring the particular needs and challenges among women who use drugs, has

been highlighted (Bawor et al., 2015; UNODC, 2018). A report from the Office on Women's Health in the United States suggests that the practice of relying on services that were designed for men to meet the needs of women who use drugs is not appropriate (USDHHS, 2017). One factor of concern is evidence that relative to men, women tend to progress quicker from drug use to drug dependence (Back et al., 2011; Clark et al., 2015), therefore, more knowledge on risk factors associated with drug use and drug-related mortality among women, in addition to access to sex-specific treatment at an early stage, is important.

Factors that contribute to drug poisoning deaths among women are likely to be multi-faceted; therefore, a review of the nature and extent of the research that has been examined in this area is warranted. There are currently no reviews on this topic.

2.2.1 Objectives

The objective of this review was to map the extent, range, and nature of evidence in relation to drug poisoning deaths among women to inform future research, policy, and practice. In addition, this review aimed to identify gaps in knowledge for future research.

2.3 Method

The methodological five-stage framework, including the optional consultation stage, developed by Arksey and O'Malley (2005) and updated by Levac et al (2010) and Daudt et al. (2013), was used to guide this scoping review. Scoping reviews involve searching, selecting, charting, assessing and collating the literature on a specific area of research interest (Arksey and O'Malley, 2005; Levac et al., 2010; Peters et al., 2015; Tricco et al., 2016, 2018).

2.3.1 Stage 1: Identify the research question

To capture the full breadth of knowledge on the topic (Arksey & O'Malley, 2005; Levac et al., 2010), the authors sought to establish what is known from the literature about drug poisoning deaths among women, what research designs are used to study this phenomenon, and finally, what gaps remain in knowledge and policy.

2.3.2 Stage 2: Identify and retrieve relevant items

The search strategy was developed in collaboration with an information specialist and implemented in May 2018 with search engine alerts maintained up to 02 November 2019. Bibliographic databases: MEDLINE, Embase, CINAHL and Web of Science were searched for relevant publications between June 1, 1998 and November 2, 2019 (Appendix 2.4 Supplementary Table C MEDLINE search strategy). This search was supplemented by searches of gray literature, searches of relevant websites such as that of the EMCDDA (http://www.emcdda.europa.eu/), receipt of updates from specialised libraries (such as the Health Research Board [HRB] National Drugs Library [http://www.drugsandalcohol.ie/]), searches of and attendance at conference/event; as well as through consultation with experts in the area. All results were imported into and managed using Endnote bibliographic management software.

The inclusion and exclusion criteria for the scoping review were developed through an iterative process as the series of searches progressed. There are various definitions used internationally for drug-related deaths. For this scoping review, *drug poisoning deaths* include all manners of death (among women) directly attributable to the toxic effects of drugs, otherwise known as “direct drug induced” or “overdose” deaths.

Publications identified were assessed as follows: The criteria for inclusion involved identifying literature that contained data on drug poisoning deaths among women. Due to the limited number of publications identified in the early stage of the search strategy, this eligibility criterion was subsequently broadened to include all publications regardless of sex. Peer-reviewed and non-peer reviewed publications were included if they were published between June 1, 1998 and November 2, 2019, were written in English, and involved humans.

Nonfatal drug poisonings, fatal poisonings related only to alcohol and/or tobacco, and mortality within randomised controlled clinical trials or attributable to medical errors were excluded. Other nondrug poisoning deaths among people who use drugs were excluded. This included, for example, deaths due to trauma or medical causes such as liver disease or human immunodeficiency virus infection. Epidemiological publications which failed to stratify drug poisoning death results by sex were excluded.

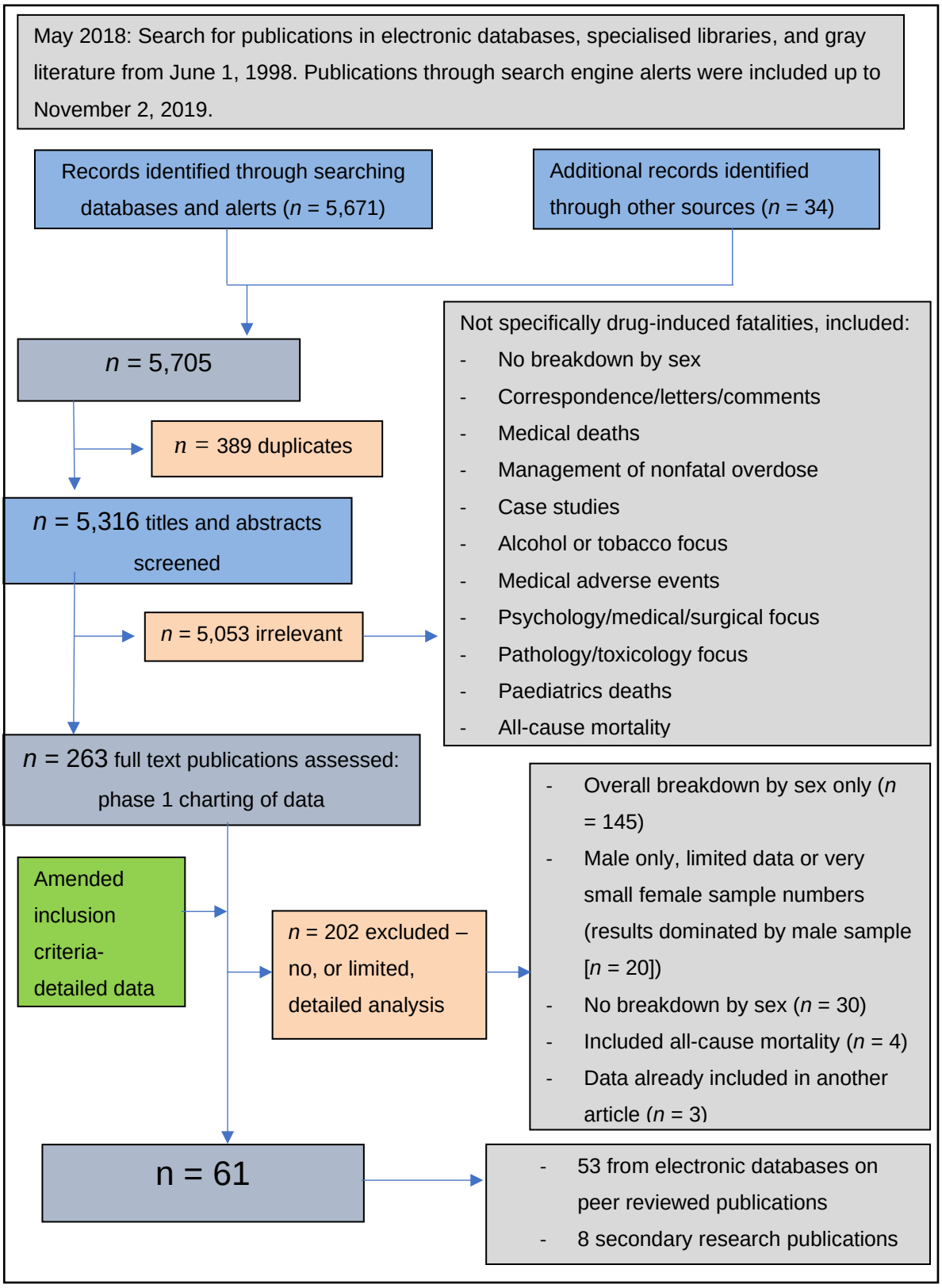

Figure 2.1 Selection of sources of evidence

2.3.3 Stage 3: Study selection (Figure 2.1)

Titles and abstracts were reviewed by one reviewer (EL) to determine potential eligibility. A second reviewer (AD) then reviewed all excluded titles and abstracts to ensure accuracy. Full text publications were then reviewed independently by two reviewers (EL, AD). Any uncertainty in relation to publication eligibility was resolved through discussion with the other authors. A consensus was reached on a final selection of publications (Figure 2.1).

2.3.4 Stage 4: Charting the data

The publications (*n* = 263) were examined and sorted according to key issues and candidate factors emerging. The first reviewer (EL) charted key data from the fully reviewed publications using a data charting form. The format of these tables and the data identified for extraction were informed by the purpose of the scoping review and, as with the other stages, this was an iterative process, progressing as the charting of this scoping review developed. Literature was then excluded if the reviewers agreed that there was insufficient data on the topic. Data charted included author, year of publication, aim of study, study design, nature of sample, drugs involved, definition of drug poisoning death, key findings, and theme for exclusion. The final selection of 61 items was agreed for inclusion.

2.3.5 Stage 5: Collating, summarising, and reporting

As recommended by Arksey and O'Malley (2005), the authors did not assess the quality of the evidence included. Instead, a narrative account of the findings was presented, including basic descriptive analysis and thematic outcomes developed from key findings. Numerical analysis included geographical distribution, drugs involved, and study design of the publications included. Data from the included publications was initially coded according to the drug(s) involved in the reported deaths. Subsequent analysis of the papers identified a number of further relevant issues associated with drug poisoning deaths among women, which were coded using the data charting form. Finally, these codes were used to construct a number of candidate factors which appear to be associated with drug poisoning deaths among women. Publications could have more than one candidate factor identified from key findings. In addition, gaps in research and considerations for policy and

practice to help decrease drug poisoning deaths among women were extracted from the data to be presented separately.

2.3.6 Stage 6: Consultation exercise

Consultations took place with national experts from the Irish National Drug-Related Deaths Index Steering Committee and international experts from the EMCDDA, which provided references for review and insights into issues associated with drug poisoning deaths among women not found in the literature.

2.4 Results

To present a narrative account of the results extracted from the final 61 publications, the following subheadings derived at the data charting stage were used: methodological issues; drugs involved in poisoning deaths among women; individual characteristics; external factors; gaps in research, and considerations for policy and practice. Almost half of publications included (*n* = 28, 46%) contained data from studies carried out in European countries, followed by the United States (*n* = 24, 39%) and Canada (*n* = 5, 8%). Two thirds (*n* = 66%) of publications were published since 2013. Publications recommended from the consultation exercise were captured through the searches. However, this consultation exercise provided valuable insight on issues and stimulated discussion on future research collaboration.

2.4.1 Study design

The majority of publications included primary research (*n* = 50, 82%) (Table 2.1 & Appendix 2.2 Supplementary Table A) involving retrospective descriptive statistical analysis drawn from surveillance systems, capturing the epidemiological trends of drug-related deaths. For the purpose of this review, surveillance systems include coronial/medical examiner data, national vital statistics on mortality, and/or toxicology data. Secondary research consisted of national and international reports and government agency reports (*n* = 7, 11%), scoping reviews (*n* = 2, 3%), 1 conference abstract and 1 editorial article (Table 2.1 & Appendix 2.3 Supplementary Table B).

2.4.2 Drugs involved in poisoning deaths among women

Opioids were the main drugs reported to be involved in poisoning deaths among women (Table 2.1). However, opioid drug poisoning deaths was the exclusive focus of 22 (36%) publications, the majority (*n* = 17, 77%) of which involved primary studies; more than half were based in the United States (*n* = 13, 59%) and just over half (*n* = 12, 55%) were published since 2015 (Appendices 2.2 and 2.3 Supplementary Tables A & B).

Findings from 25 (41%) publications, for which the focus was not exclusively on opioid poisoning deaths, suggested that opioids, especially prescription opioids, either alone or in combination with other drugs including alcohol, were prominent in drug poisoning deaths among women. Almost all (*n* = 24, 96%) were from primary studies and 12 (48%) originated in Europe (Appendices 2.2 and 2.3 Supplementary Tables A & B).

Eighteen publications (30%) suggested the presence or overrepresentation of antidepressants in poisoning deaths among women (Table 2.1). The majority of these publications (*n* = 13, 72%) were before 2014. The presence or overrepresentation of benzodiazepines in poisoning deaths among women was suggested in 14 publications (23%) (Table 2.1). The majority of these publications (*n* = 9, 64%) were before 2014. However, evidence from more recent publications suggest that antidepressant drugs and benzodiazepines are still candidate factors in drug poisoning deaths among women (Austin et al., 2017; VanHouten et al., 2019).

The involvement of more than one drug (polydrug use) as a candidate factor for drug poisoning deaths among women was suggested in 14 (23%) publications. The involvement of polydrugs was suggested by one primary study to be more prominent in poisoning deaths among women who had a history of chronic pain relative to women without chronic pain (Szymanski et al., 2016).

2.4.3 Individual characteristics

2.4.3.1 Age profile (n = 33, 54%)

More than half of the publications included age profile (*n* = 33, 54%). Nine primary studies reported findings of women being older than men among drug poisoning deaths, with Wunsch et al. (2009), and Gjersing et al. (2013) reporting a higher mean age by 4 years for women relative to men at time of death. A variety of

age profiles at time of death were presented, especially if different drugs were involved in poisoning deaths; with six studies suggesting an increased risk of drug poisoning death among women linked to an increase in age (Shah et al., 2001b; Taylor, 2016; Tweed et al., 2018), especially if opioids (Advisory Council on the Misuse of Drugs [ACMD], 2016; Gao et al., 2016; Pierce et al., 2015), were involved.

The majority (*n* = 27, 82%) of articles that included age profiles involved retrospective secondary data analysis of epidemiological surveillance systems (Appendices 2.2 and 2.3 Supplementary Table A and B). Twenty (61%) publications originated in Europe (Appendices 2.2 and 2.3 Supplementary Table A and B).

2.4.3.2 Mental health (n = 9, 15%)

Mental health issues, especially anxiety and/or depression, were reported as possible candidate factors in 15% (*n* = 9) of publications. More than half (*n* = 5, 56%) of these publications were from secondary research (Barnsdale et al., 2018; Clark et al., 2015; Ireland Department of Health, 2017; Tweed et al., 2018; UNODC, 2018). A history of a non-fatal poisoning was also suggested as a candidate factor for fatal poisonings among women (Sinyor et al., 2012).

2.4.3.3 Intentional (suicide) drug poisoning death (n = 14, 23%)

In the subset of studies identified, women tend to be overrepresented in publications that included suicide deaths as a result of drug poisoning (Barnsdale et al., 2018; Värnik et al., 2011), but this may not be representative of all such studies. Age older than 45 years was suggested to be a candidate factor in suicide drug poisoning deaths for women (Appendices 2.2 and 2.3 Supplementary Table A and B).

The main drugs involved in suicide poisoning deaths were reported to be opioids and/or antidepressants (Austin et al., 2017; Barnsdale et al., 2018; Gladstone et al., 2016; Isacsson et al., 1999; Oyefeso et al., 2000; Shah et al., 2002; Wunsch et al., 2009). Almost all (*n* = 12, 86%) of the publications that reported on the topic of suicide drug poisonings involved retrospective secondary data analysis of epidemiological surveillance systems.

2.4.3.4 Treatment for drug use (n = 11, 18%)

The protective factor of treatment, including decreased risk of drug poisoning death for people who use drugs, was documented (Gjersing & Bretteville-Jensen, 2014; Ireland Department of Health, 2017; Lovrecic et al., 2013; Oyefeso et al., 2000). Two primary studies suggest a candidate factor for drug poisoning deaths among women was to have dropped out of drug treatment (Petrushevska et al., 2015; Quaglio et al., 2001). One technical report suggested that because of barriers women may encounter in accessing treatment - including stigma, lack of social supports including childcare, and lack of flexibility and accessibility in services - women in the general population with substance use disorder may be less likely to be able to access treatment (UNODC, 2018). Considering barriers women may encounter in accessing treatment, the need to provide sex-specific treatment was emphasised (Diamond, 2018; Hayashi et al., 2016; Ireland Department of Health, 2017; Tweed, et al., 2018; USDHHS, 2017).

Although the majority (*n* = 6, 55%) of publications reporting on the theme of treatment involved retrospective secondary data analysis from surveillance systems, the remainder, with more detailed information, came from the secondary research, which included a scoping review (Tweed et al., 2018) and reports/policy documents (Ireland Department of Health, 2017; UNODC, 2018; USDHHS, 2017).

2.4.3.5 Differences in biological reactions to drugs between sexes (n = 8, 13%)

The studies (*n* = 8, 13%) highlighting the influence of biological differences between men and women were more commonly reported in the secondary research (*n* = 5, 63%) included in this review. It is reported that men and women vary in multiple aspects of addiction characteristics including biological differences (Algren et al., 2013) and specific risk factors. Algren et al (2013) reported pharmacokinetic sex-related differences in opioid response, which suggests that women who use opioids experience a more pronounced clinical effect and a greater risk of toxicity. Goa et al. (2016) highlighted the specific cardiac effects for women using methadone, including effects on the electrical conductivity of the heart muscle, which can put these women at risk of sudden cardiac death.

Women also tend to have a faster escalation from onset of drug use to problematic use and drug poisoning death relative to men (Clark et al., 2015; Diamond, 2018; Origer et al., 2014; UNODC, 2018; USDHHS, 2017).

Table 2.1 Characteristics of evidence from 61 publications included

Type of evidence	**Primary research**	**Technical reports**	**Scoping reviews**	**Conference abstracts**	**Editorials**
Number of publications (Reference(s))	**50** (Isacsson et al., 1999; Oyefeso et al., 2000; Shah et al., 2001a; Shah et al., 2001b; Quaglio et al., 2001; Shah et al., 2002; Preti et al., 2002; Bird et al., 2003; Davidson et al., 2003; Gunnell et al., 2004; Bryant et al., 2004; Shah et al., 2005; Morgan et al., 2006; Shah et al., 2008; Wunsch et al., 2009; Piercefield et al., 2010; Green et al., 2011; Värnik et al., 2011; Zamparutti et al., 2011; Bird & Robertson, 2011; Sinyor et al., 2012; Origer et al., 2014; Algren et al., 2013; Gjersing et al., 2013; Mack et al., 2013; Lovrecic et al., 2013; Binswanger et al., 2013; Calcaterra & Binswanger, 2013; Borriello et al., 2014; Rudd et al., 2014; Gjersing & Bretteville-Jensen, 2014; Hassanian-Moghaddam et al., 2014; Pierce et al., 2015; Roxburgh et al., 2015; Petrushevska et al., 2015; Gladstone et al., 2016; Hayashi et al., 2016; Metz et al., 2016; Gao et al., 2016; Szymanski et al., 2016; Groot et al., 2016; Austin et al., 2017; Roxburgh et al., 2017; Bukten et al., 2017; Pizzicato et al., 2018; Nechuta et al., 2018; Jalal et al., 2018; Gomes et al., 2018; Scholl et al., 2019; VanHouten et al., 2019)	**7** (CDC, 2013; Clark et al., 2015; USDHHS, 2017; Taylor, 2016; Ireland Department of Health, 2017; Barnsdale et al., 2018; UNODC, 2018)	**2** (ACMD, 2016; Tweed et al., 2018)	**1** (Iwanicki et al., 2015)	**1** (Diamond, 2018)

Origin of evidence	**Europe**	**United States**	**Canada**	**Australia**	**Middle East**	**United Nations**

Number of publications (Reference(s))	**28** (Isacsson et al., 1999; Oyefeso et al., 2000; Shah et al., 2001a; Shah et al., 2001b; Quaglio et al., 2001; Shah et al., 2002; Preti et al., 2002; Bird et al., 2003; Gunnell et al., 2004; Morgan et al., 2006; Värnik et al., 2011; Zamparutti et al., 2011; Bird & Robertson, 2011; Origer et al., 2014; Gjersing et al., 2013; Lovrecic et al., 2013; Borriello et al., 2014; Gjersing & Bretteville-Jensen, 2014; Pierce et al., 2015; Petrushevska et al., 2015; Gao et al., 2016; Bukten et al., 2017; Clark et al., 2015; Taylor, 2016; ACMD, 2016; Ireland Department of Health, 2017; Tweed et al., 2018; Barnsdale et al., 2018)		**24** (Davidson et al., 2003; Bryant et al., 2004; Shah et al., 2005; Shah et al., 2008; Wunsch et al., 2009; Piercefield et al., 2010; Green et al., 2011; Algren et al., 2013; Mack et al., 2013; Binswanger et al., 2013; Calcaterra & Binswanger, 2013; Rudd et al., 2014; Metz et al., 2016; Szymanski et al., 2016; Austin et al., 2017; Pizzicato et al., 2018; Nechuta et al., 2018; Jalal et al., 2018; Scholl et al., 2019; VanHouten et al., 2019; CDC, 2013; Iwanicki et al., 2015; USDHHS, 2017; Diamond, 2018)		**5** (Sinyor et al., 2012; Gladstone et al., 2016; Hayashi et al., 2016; Groot et al., 2016; Gomes et al., 2018)	**2** (Roxburgh et al., 2015; Roxburgh et al., 2017)	**1** (Hassanian-Moghaddam et al., 2014)	**1** (UNODC, 2018)	
Themes*	**Age**	**Suicide by drug poisoning**	**Treatment for substance use disorder**	**Mental health**	**Biological differences**	**Violence**	**Incarceration**	**Sex work**	**Caregiver status**
Number of publications (References)	**33** (Shah et al., 2001a; Shah et al., 2001b; Shah et al., 2002; Preti et al., 2002; Davidson et al., 2003; Gunnell et al.,	**14** (Isacsson et al., 1999; Oyefeso et al., 2000; Shah et al., 2002; Wunsch et al., 2009; Värnik et al., 2011; Zamparutti et al.,	**11** (Oyefeso et al., 2000; Quaglio et al., 2001; Lovrecic et al., 2013; Gjersing & Bretteville-	**9** (Shah et al., 2001b; Sinyor et al., 2012; Origer et al., 2014; Roxburgh et	**8** (Algren et al., 2013; Origer et al., 2014; Clark et al., 2015; Metz et al., 2016; Gao et al., 2016; USDHHS, 2017;	**7** (Clark et al., 2015; USDHHS, 2017; Ireland Departmen	**6** (Binswanger, 2013; Groot et al., 2016; Bukten et al., 2017; UNODC,	**3** (Origer et al., 2014; Gjersing & Brettevill e-	**2** (USDH HS. 2017; UNODC . 2018)

	2004; Morgan et al., 2006; Wunsch et al., 2009; Piercefield et al., 2010; Värnik et al., 2011; Zamparutti et al., 2011; Sinyor et al., 2012; Algren et al., 2013; Gjersing et al., 2013; CDC, 2013; Calcaterra & Binswanger, 2013; Borriello et al., 2014; Petrushevska et al., 2015; Roxburgh et al., 2015; Pierce et al., 2015; Metz et al., 2016; Gao et al., 2016; Taylor, 2016; ACMD, 2016; Szymanski et al., 2016; Groot et al., 2016; Austin et al., 2017; Tweed et al., 2018; Nechuta et al., 2018; Jalal et al., 2018; Diamond,	2011; Sinyor et al., 2012; ; Roxburgh et al., 2015; Gladstone et al., 2016; Szymanski et al,. 2016; Austin et al., 2017; Tweed et al., 2018; Barnsdale et al., 2018; Diamond, 2018)	Jensen, 2014; Petrushevska et al., 2015; Hayashi et al., 2016; USDHHS, 2017; Ireland Department of Health, 2017; Tweed et al., 2018; Barnsdale et al., 2018; UNODC, 2018; Diamond, 2018)	al., 2015; Clark et al., 2015; Ireland Department of Health, 2017; Barnsdale et al., 2018; Tweed et al., 2018; UNODC, 2018)	UNODC, 2018; Diamond, 2018)	t of Health, 2017; Barnsdale et al., 2018; Tweed et al., 2018; UNODC, 2018; Diamond, 2018)	2018; Pizzicato et al., 2018; Diamond, 2018)	Jensen, 2014; UNODC, 2018)	

	2018; Scholl et al., 2019; VanHouten et al., 2019)								
Main drugs involved in poisoning deaths*	**Opioids**	**Antidepressants**	**Benzodiazepines / tranquillizers**	**Paracetamol**	**Psychostimulants**	**Cocaine**	**Any illicit drugs**	**Polydrug use**	
Number of publications (Reference(s))	**47** (Quaglio et al., 2001; Shah et al., 2001b; Shah et al., 2002; Preti et al., 2002; Bird et al., 2003; Davidson et al., 2003; Bryant et al., 2004; Shah et al., 2005; Morgan et al., 2006; Shah et al., 2008; Wunsch et al., 2009; Piercefield et al., 2010; Green et al., 2011; Zamparutti et al., 2011; Bird & Robertson, 2011; Sinyor et al., 2012; Algren et al., 2013;	**18** (Isacsson et al., 1999; Oyefeso et al., 2000; Shah et al., 2001a; Shah et al., 2001b; Shah et al., 2002; Gunnell et al., 2004; Wunsch et al., 2009; Green et al., 2011; Sinyor et al., 2012; Origer et al., 2014; Mack et al., 2013; CDC, 2013; Binswanger et al., 2013; Petrushevska et al., 2015; Clark et al., 2015; Austin et al., 2017; Barnsdale et al., 2018;	**14** (Shah et al., 2001b; Shah et al., 2002; Preti et al., 2002; Bird et al., 2003; Gunnell et al., 2004; Wunsch et al., 2009; Bird & Robertson, 2011; Mack et al., 2013; Binswanger et al., 2013; Petrushevska et al., 2015; Clark et al., 2015; Austin et al., 2017; Nechuta et al., 2018;	**4** (Shah et al., 2002; Shah et al., 2001b; Gunnell et al., 2004; ACMD, 2016)	**1** (Calcaterra & Binswanger, 2013)	**9** (Preti et al., 2002; Shah et al., 2008; Binswanger et al., 2013; Origer et al., 2014; Borriello et al., 2014; Austin et al., 2017; Jalal et al., 2018; Scholl et al., 2019; VanHouten	**23** (Quaglio et al., 2001; Preti et al., 2002; Bryant et al., 2004; Shah et al., 2005; Morgan et al., 2006; Algren et al., 2013; Origer et al., 2014; Gjersing et al., 2013; Mack et al., 2013; Lovrecic et al., 2013; Binswanger	**14** (Oyefeso et al., 2000; Preti et al., 2002; Shah et al., 2005; Shah et al., 2008; Green et al., 2011; Gjersing et al., 2013; Mack et al., 2013; Origer et al., 2014; Borriello et al., 2014; Gjersing & Bretteville-Jensen, 2014; ACMD, 2016; Szymanski et al., 2016; Nechuta et al., 2018; Tweed et al., 2018)	

	Origer et al., 2014; Gjersing et al., 2013; Mack et al., 2013; Lovrecic et al., 2013; CDC. 2013; Binswanger et al., 2013; Rudd et al., 2014; Gjersing & Bretteville-Jensen, 2014; Borriello et al., 2014; Iwanicki et al., 2015; Hassanian-Moghaddam et al., 2014; Petrushevska et al., 2015; Roxburgh et al., 2015; Pierce et al., 2015; Gladstone et al., 2016; Metz et al., 2016; Gao et al., 2016; ACMD, 2016; Szymanski et al., 2016; Groot et al., 2016; USDHHS, 2017; Austin et al., 2017; Roxburgh et al., 2017; Barnsdale	VanHouten et al., 2019)	VanHouten et al., 2019)			et al., 2019)	et al., 2013; Rudd et al., 2014; Petrushevska et al., 2015; Hayashi et al., 2016; Metz et al., 2016; Gao et al., 2016; ACMD, 2016; Taylor, 2016; Austin et al,. 2017; Tweed et al., 2018; Jalal et al., 2018; Scholl et al., 2019; VanHouten et al., 2019)	

	et al., 2018; Nechuta et al., 2018; Jalal et al., 2018; Gomes et al., 2018; Diamond, 2018; Scholl et al., 2019; VanHouten et al., 2019)							

2.4.4 External factors

2.4.4.1 Violence against women (n = 7, 11%)

Violence and/or sexual abuse was highlighted as a candidate factor in seven (11%) publications. It was suggested that women who died of drug poisoning deaths were more likely than men to have experienced domestic violence or sexual abuse (Barnsdale et al., 2018; Diamond, 2018; UNODC, 2018). Domestic violence may be a risk factor and/or a consequence of drug use (Clark et al., 2015; USDHHS, 2017) and could potentially make recovery more difficult (Tweed et al., 2018); therefore, increased awareness of the implications of domestic violence in the treatment and rehabilitation of women who use drugs was recommended (Ireland Department of Health, 2017). The majority (*n* = 5, 71%) of the publications reporting on the theme of violence came from secondary research (Appendix 2.3 Supplementary Table B).

2.4.4.2 Sex work (n = 3, 5%)

In addition to some women depending on sex work to fund their drug use (Origer et al., 2014), two publications identified being involved in sex work as a candidate factor for drug poisoning deaths among women (Gjersing & Bretteville-Jensen, 2014; UNODC, 2018).

2.4.4.3 Incarceration (n = 6, 10%)

Incarceration was highlighted as a candidate factor in six (10%) publications, with the majority (*n* = 5, 83%) from primary studies. Two secondary research publications reported a high proportion of women incarcerated for drug-related offences (UNODC, 2018) with a high proportion of women prisoners likely to have substance use disorder (Diamond, 2018). The risk of drug poisoning death following release from prison was found, using retrospective cohort study data linked to mortality data, to be high for women (Binswanger et al., 2013; Pizzicato et al., 2018), especially younger women (20-29 years) (Groot et al., 2016), and within six months of release (Bukten et al., 2017). Four primary studies suggested the opportunity to provide public health interventions, including overdose education and opioid substitution treatment, to a prison population should be availed of, including the provision of naloxone upon release and linkage to both social and health services

following release (Binswanger et al., 2013; Bukten et al., 2017; Groot et al., 2016; Pizzicato et al., 2018).

2.4.4.4 Carer status (n = 2, 3%)

A small number of secondary research publications (*n* = 2, 3%) highlighted carer status as a candidate factor. Women tended to be the main carers of children, and thus a premature drug poisoning death of a mother will have negative effects on both their children and society (UNODC, 2018). This was further emphasised in the consultation phase with a family support group (National Family Support Network), who highlighted the negative effects on all family members following drug poisoning deaths.

Treatment for drug use is recognised as a protective factor against drug poisoning deaths; therefore, women with children who wish to access treatment should have childcare needs addressed (Ireland Department of Health, 2017; USDHHS, 2017).

2.5 Discussion

The overall objective of this review was to explore what is already known from existing evidence on drug poisoning deaths among women and to identify the gaps in knowledge for further research. The majority of the published research reviewed on drug poisoning deaths among women were based on surveillance systems that captured epidemiological trends but lacked inclusion of more in-depth adjusted analysis or investigation of factors explaining these trends. Where these factors were explored, they generally lacked stratification by sex. Of these primary studies, the majority originated from Europe (*n* = 22, 44%), followed by the United States (*n* = 20, 40%). There was a very obvious geographical difference for specific drug groups. The majority of primary research from the United States included in this review focused on, or the main findings related to, opioid poisoning deaths (*n* = 18, 90%). Primary research from Europe included a wider range of drugs involved in poisoning deaths, including opioids but also prescription drugs such as benzodiazepines and antidepressants.

More research is required using large samples, as the deficit of in-depth sex-specific research may mask identifying potential risk factors for women because of the prominence of men in drug poisoning deaths (Masters et al., 2017).

Most literature reviewed focused on opioids, especially polydrug poisoning deaths where opioids were involved. Sex-specific differences in pharmacokinetics for certain drugs, including opioids and benzodiazepines (Whitley & Lindsey, 2009), may be having more of an impact on polydrug poisoning deaths among women. Given the prominence of polydrugs in drug poisoning deaths among women, further sex-specific research into factors influencing polydrug poisoning deaths and deaths involving non-opioid drugs will enhance our knowledge in this area, as limited information was ascertained through this review.

Relative to men, women tend to use nonviolent methods of suicide, with drug poisoning death a common method of suicide by women, although this review may not be representative of all evidence in this area. As suggested by Sinyor et al (2012), a key element to influencing public health policy in decreasing suicides is to increase knowledge on the specific drugs involved in suicides. More women-focused analysis on specific drugs involved as well as exploring other possible candidate factors in this area would be beneficial.

Although there are more men than women in prisons, since 2007 there has been a greater decline in the rate of men being incarcerated than women (Bronson & Carson, 2019), especially for drug-related offences (UNODC, 2018). Being in receipt of opioid substitution treatment in prison and after release is associated with a reduction in drug poisoning deaths (Degenhardt et al., 2014; Marsden et al., 2017). Because a high proportion of women prisoners are likely to have substance use disorder (Diamond, 2018), access to treatment is imperative to help decease these drug poisoning deaths after release.

2.5.1 Gaps in research and considerations for policy and practice

The need for more sex-specific analysis in relation to drug poisoning deaths and associated risk factors has been previously highlighted (Barnsdale et al., 2018; Bird et al., 2003; Origer et al., 2014; Tweed et al., 2018; USDHHS, 2017) and was further emphasised from experts through the consultation exercise. Gaps in research highlighted in this review include drug poisoning deaths among women with co-

occurring mental health issues, women with a history of incarceration (USDHHS, 2017) and women who misuse prescription drugs (Tweed et al., 2018).

To help prevent drug poisoning deaths among women, nonmedical use of prescription drugs, in particular psychotropic drugs, has been emphasised as an area that requires urgent attention (Clark et al., 2015; Tweed et al., 2018). To monitor prescription practices and stricter availability of prescription drugs, development and use of sex-specific risk tools should be considered. These risk tools should take into consideration physiological differences between sexes in relation to pharmacokinetics and pharmacodynamics, in addition to assessment for substance abuse and mental health issues, especially when prescribing medicines such as opioids and antidepressants (Mack et al., 2013; Roxburgh et al., 2015; Szymanski et al., 2016). In addition, an online prescription monitoring database should be in place, which would allow medical practitioners to access the prescription history of individuals (Roxburgh et al., 2017).

Addressing possible barriers to accessing and remaining in treatment for substance use disorder, in addition to taking a trauma-informed approach to treatment, may provide the most appropriate type of treatment, including psychological treatment, to promote stability and recovery and decrease drug poisoning deaths.

2.5.2 Strengths and limitations

To the best of the authors' knowledge, this is the first scoping review undertaken on drug poisoning deaths among women. A strong point of scoping reviews is the inclusion of all publications, including peer-reviewed articles and gray literature such as government reports, which can be relied on to inform policy and practice, as well as consultation with experts in the area. However, a limitation to scoping reviews is the lack of in-depth quality appraisal of the evidence. The search was limited to publications in the past twenty-one years (1998-2019); therefore, it is possible that potentially relevant publications before 1998 could have been missed. Where publications included statistical analysis, they mainly consisted of descriptive unadjusted statistical analysis. Only five publications selected used multivariable modelling to identify sex-specific differences related to poisoning deaths.

Five of the primary studies contained a small sample size of women compared to the sample size of men, thus limiting their power to investigate specific factors pertaining to drug poisoning deaths among women.

2.5.3 Conclusion

From the studies reviewed, the majority of data available on drug poisoning deaths among women was epidemiological trends with limited in-depth analysis of factors explaining these trends. Within the studies reviewed, there is a dearth of knowledge exploring the contribution of candidate factors or a combination of these factors to drug poisoning deaths among women. Such a gap in empirical analysis deprives policy makers from building meaningful interventions that might target the most significant factors and relationships of factors that may prevent such deaths among women. To prevent drug poisoning deaths among women, it is important to investigate risk factors and the different drugs involved and to tailor policies and practices accordingly.

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Chapter 3: Trends in drug poisoning deaths, by sex, in Ireland: a repeated cross-sectional study from 2004 to 2017

The chapter is based on the paper: Lynn, E., Cousins, G., Lyons, S., & Bennett, K.E. (2021). Trends in drug poisoning deaths, by sex, in Ireland: a repeated cross-sectional study from 2004 to 2017. *BMJ Open,* 11**,** e048000. https://doi:10.1136/bmjopen-2020-048000

Study aim

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, and (3) individual drugs/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.

Author contributions

EL, KB, and GC contributed to the concept and design of the study. EL and KB, 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, agreed to be accountable for all aspects of the work, and approved the final manuscript.

Corresponding publication

A summary article related to this publication was written by EL and published in Drugnet Ireland (Appendix 3.1).

3.1 Abstract

Objective: To 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: The primary outcome was trends in drug poisoning death rates by sex. The secondary outcomes were trends in drug poisoning death rates involving (1) any CNS (Central Nervous System) depressants, (2) ≥ 2 CNS depressants and (3) specific drugs/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.

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.

3.2 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(Shiels et al., 2020). During this period drug poisoning death rates increased in most U.S. states, primarily due to synthetic opioids (Scholl et al., 2019). Drug poisoning deaths involving psychostimulants, especially cocaine, have also increased in the U.S. (McCall et al., 2017; Seth et al., 2018). Accidental drug poisonings are predicted to be a leading cause of premature deaths in the U.S. over the next decade, especially among women (Best et al., 2018). Drug poisoning deaths have also increased in Australia since 2006, with opioids being the most common drug group involved in these deaths (Man et al., 2019).

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 (Kimber et al., 2019). 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 (EMCDDA, 2014), to 22.6 deaths per million population aged 15-64 years in 2018 (EMCDDA, 2020). Opioids (both licit and illicit), commonly heroin, are involved in approximately 8 out of every 10 drug poisoning deaths reported in Europe (EMCDDA, 2020). However, postmortem toxicology analyses of poisoning deaths suggest that multiple drug toxicity is implicated in most deaths (EMCDDA, 2020).

While sex differences in drug poisoning deaths have emerged in recent years (Jalal et al., 2018), most of the available evidence fails to account for variation by sex regarding drugs involved (Lynn et al., 2020). 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 (Jalal et al., 2018). In contrast, in both the U.S. and Scotland, risk of drug poisoning deaths among older women were attributed to prescription opioids,

antidepressants (Centers for Disease Control and Prevention, 2013; Tweed, 2018), and unspecified drugs (Jalal et al., 2018). Many drug poisoning deaths involve a fatal cocktail of CNS depressant drugs (Corkery et al., 2004; Health Research Board, 2019). Sex-specific differences in pharmacokinetics for CNS depressant drugs such as opioids (Algren et al., 2013), pregabalin and benzodiazepines (Whitley & Lindsey, 2009), 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 (EMCDDA, 2020; Osborn, 2018; VanHouten et al., 2019), especially in relation to intentional drug poisoning deaths (Tyrrell et al., 2017).

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 drugs/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.

3.3 Methods

The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist for cross-sectional studies (STROBE Statement, 2007), 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.

3.3.1 Patient and public involvement

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

3.3.2 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 (Lynn et al., 2009). It follows the EMCDDA standard protocol to collect data on drug-related deaths (EMCDDA, 2010). 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 (Roxburgh et al., 2018). 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 (Lynn et al., 2009). 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 (Health Research Board, 2019).

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 Service (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 (Sinnott et al., 2017). 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 (Sinnott et al., 2017). As of 2015, almost 40% of the Irish population were covered by the GMS scheme (Sinnott et al., 2017).

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 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.

3.3.3 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 drugs/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.

3.3.4 Statistical analysis

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

3.3.4.1 Drug poisoning deaths

Irish general population estimates were extracted from the CSO for calculation of rates of drug poisoning deaths per 100,000 population (Central Statistics Office, 2020). For prescription rates the GMS eligible population for those aged 16 years and older was extracted from the PCRS annual reports (Health Service Executive, 2021). The European Standard Population (ESP) was used to calculate age-standardised rates (ASR) (Eurostat, 2013).

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 (Central Statistics Office, 2020), standardised to the European Standard Population (ESP) (Eurostat, 2013). 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 (National Cancer Institute, 2020) 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 drugs/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.

3.3.4.2 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.).

3.4 Results

3.4.1 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 3.1). However, there was no significant change among women for the same period (Table 3.2). 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 3.1).

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 3.1 (men) and 3.2 (women).

3.4.2 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 3.3). 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 3.1).

For women who died of drug poisoning 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 3.2).

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.

3.4.3 Prescription opioids

All drug poisoning deaths involving prescription opioids, of which 61% consisted of methadone, have increased over time (Table 3.3) 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 3.1 & 3.2). 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.

3.4.4 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

3.1) and 3.3% (95% CI, 0.1 – 6.5) among women (Table 3.2) with no change points, indicating no change in trend(s) within the reporting period, observed for either men or women (Table 3.1 & Table 3.2). 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 3.1) 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 3.1). However, this relationship was not statistically significant for women.

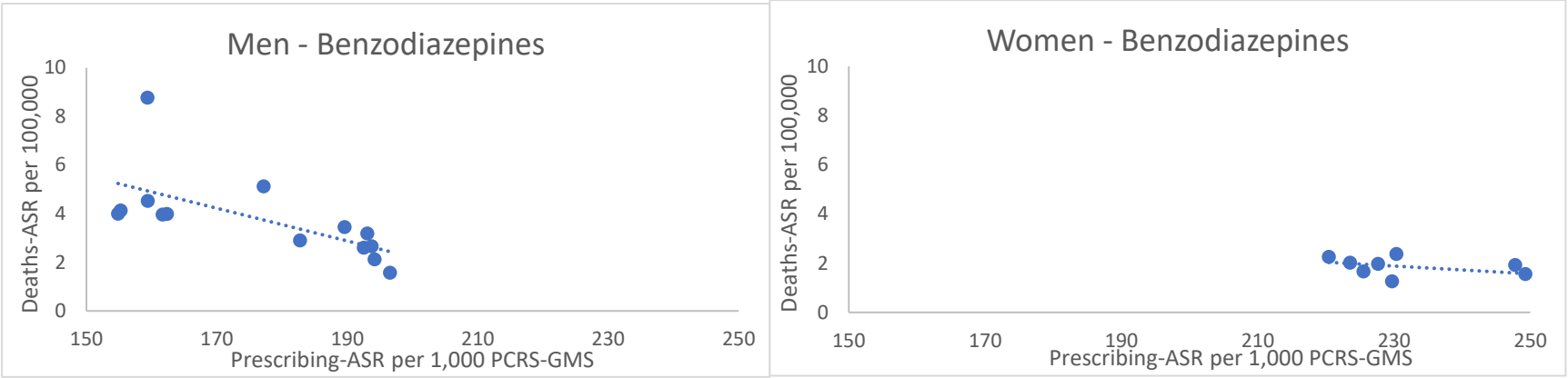

Figure 3.1 Benzodiazepines: Age-standardised rates per 100,000 of drug poisoning deaths involving benzodiazepines and age-standardised rates per 1,000 of individuals in receipt of prescribed benzodiazepines through the PCRS-GMS; 2004 to 2017.

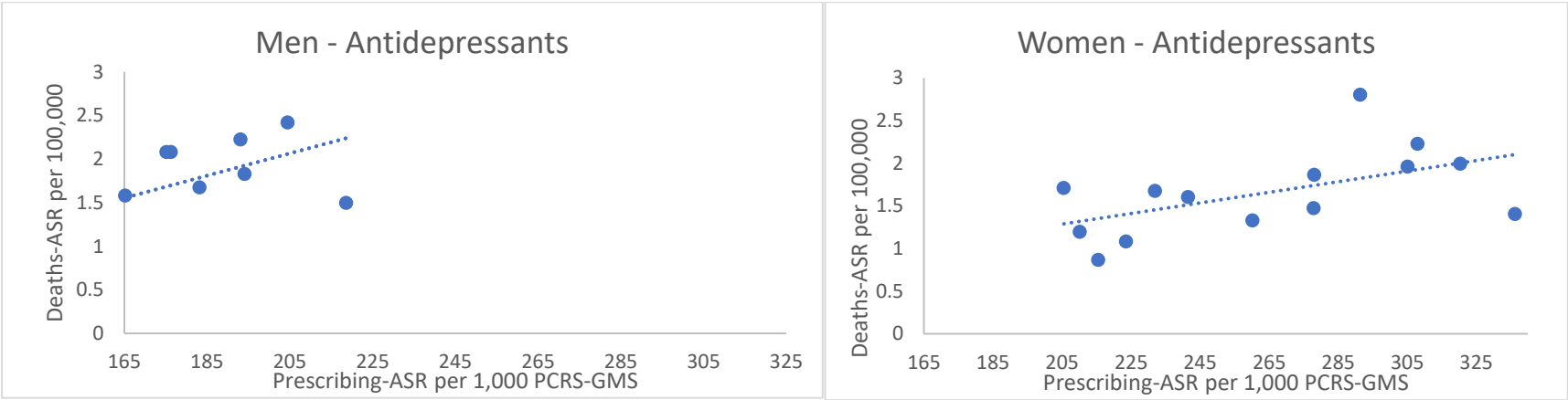

Figure 3.2 Antidepressants: Age-standardised rates per 100,000 of drug poisoning deaths involving antidepressants and age-standardised rates per 1,000 of individuals in receipt of prescribed antidepressants through the PCRS-GMS; 2004 to 2017.

3.4.5 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 3.1 & Table 3.2). There were no change points, indicating no change in trend(s) within the reporting period observed (Tables 3.1 & Table 3.2). 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 reporting 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 ($\beta = 0.013$, [95% CI 0.003, 0.022], $p = 0.011$) and women ($\beta = 0.006$, [95% CI 0.000, 0.012], $p = 0.045$) (Figure 3.2). 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).

3.4.6 Alcohol

The rate for women who died of drug poisoning involving alcohol decreased with an AAPC decrease of 4.0% (95% CI, -5.8 – -2.1) between 2004 and 2017 (Table 3.2). There was no statistically significant AAPC in rates for men in the same period (Table 3.1). 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 3.1). 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%).

3.4.7 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 3.1). 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 3.2). 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 8.36 in 2004 to 2.67 in 2017 (Table 3.3).

3.4.8 Heroin

No trend change, for either sex, was observed for drug poisoning deaths involving heroin over the study period (Tables 3.1 & Table 3.2). 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 3.3).

Table 3.1 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 3.2 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
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 3.3 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)

3.5 Discussion

3.5.1 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 (Scholl et al., 2019). In Ireland, while drug poisoning deaths involving

prescription opioids have increased, deaths involving fentanyl remain very low (Health Research Board, 2019). 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 (Lynn et al., 2020). 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. (Corkery et al., 2004), with women disproportionately affected. Compared to men, a higher percentage of women who died from drug poisoning involving methadone were registered for OAT at the time of their death, even though fewer women receive OAT in Ireland (Cousins et al., 2017). A growing body of evidence suggests that mortality risk during OAT is time varying (Sordo et al., 2017). 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 (Cousins et al., 2011; Durand et al., 2020; Evans et al., 2015; Sordo et al., 2017). 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 (Cousins et al., 2011; Durand et al., 2020; Evans et al., 2015; Kimber et al., 2015). 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 while registered on the OAT register had in fact left treatment because global evidence clearly demonstrates the protective effects of treatment versus leaving treatment (Santo et al., 2021). 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 (Jarlenski et al., 2017). Polydrug use, especially opioids with sedative drugs, including benzodiazepines, have been associated with active post-traumatic stress disorder (Hassan & Le Foll, 2019), and with serious health risks including drug poisoning deaths (Calcaterra et al., 2013).

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 (Lynn et al., 2020).

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 (Affleck et al., 2018). 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 (Affleck et al., 2018). 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 (National Advisory Committee on Drugs and Alcohol, 2016). 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 (Norström & Mäkelä, 2019). Per capita consumption of alcohol in Ireland decreased during the study period.(Revenue Commissioners, 2020). 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, (Government of Ireland, 2018) 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 (Eurostat, 2020). 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 (Hedegaard et al., 2020), 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 (National Advisory Committee on Drugs and Alcohol, 2016). In addition, in recent years there has been an increase in people seeking treatment related to cocaine use (EMCDDA, 2020), with an increase in the proportion of

women in receipt of treatment for cocaine during the latter years of the study (O'Neill et al., 2020). 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.

3.5.2 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 (Algren et al., 2013; Whitley & Lindsey, 2009). Similar to that reported in other European countries (Novak et al., 2016), 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 (Benzodiazepine Committee, 2002). 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 (Duffin et al., 2020), 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 (Ryan, 2020). 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 (O'Carroll et al., 2021). 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 (O'Neill et al., 2020). While it is unknown what proportion of drug poisoning deaths since 2017 involved benzodiazepines, the United Nations Office on Drugs and Crime (UNODC, 2017), 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 (Lynch et al., 2020). 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 (Lynch et al., 2020).

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 (National Advisory Committee on Drugs and Alcohol, 2016). It is known that between 2010 and 2011 there was a severe shortage of heroin in the European market (EMCDDA, 2011), 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 (Health Research Board, 2019). 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 (Roxburgh et al., 2004; Degenhardt et al., 2005).

Internationally there has been a decrease in recent years in the number of new treatment entries for OAT (EMCDDA, 2020; O'Neill et al., 2020). However, data from 2018 shows a significant increase in heroin seizures in the European Union (EMCDDA, 2020). This, in combination with recent evidence from Australia showing an increase in deaths involving heroin (Australian Institute of Health and Welfare, 2020), 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), (Pharmaceutical Society of Ireland, 2010) 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 (Degenhardt et al., 2019; Fairbairn et al., 2017). 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 (Crowley & Delargy, 2020). 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 (EMCDDA, 2017; UNODC, 2016). 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.

3.5.3 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.

3.5.4 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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Chapter 4: A repeated cross-sectional study of factors associated with pregabalin-positive poisoning deaths in Ireland

This chapter is based on the paper: Lynn, E., Cousins, G., Lyons, S. & Bennett, K.E. (2020). A repeated cross-sectional study of factors associated with pregabalin-positive poisoning deaths in Ireland. *Drug and Alcohol Dependence,* 206, 107741. https://doi:10.1016/j.drugalcdep.2019.107741

Study aim

The aim of this study is to examine factors associated with pregabalin-positive poisoning deaths, by sex, in Ireland between 2013 and 2016 in order to inform policy and practice to help reduce these deaths.

Sensitivity analysis (Appendix 4.4)

In the sensitivity analysis the sample where 'unknown' values were recoded as 'system missing' for the following variables was used: alone at time of incident that led to death, employment status, homeless. Results from the sensitivity analysis were similar to the study analysis, however some variables such as 'history of opioid misuse' and 'In treatment' showing less significant results for men.

Author contributions

EL and GC designed the study. EL was responsible for the writing of the manuscript and undertook the statistical analysis with guidance from KB and GC. All authors provided critical input to drafts of the paper. All authors contributed to the interpretation of the data and approved the final manuscript.

4.1 Abstract

Background: The increasing use of pregabalin and the presence of pregabalin in poisoning deaths, particularly with opioids, highlight it as a potential drug of abuse. In this study we examined factors associated with pregabalin-positive poisoning deaths (PPPD) between 2013 and 2016 in Ireland.

Methods: Data were extracted from the National Drug-Related Deaths Index (NDRDI). Analysis included univariate and multivariate logistic regression to estimate unadjusted and adjusted odds ratios (OR) and 95% confidence intervals (CI) for factors associated with PPPD (primary outcome) by logistic regression models for the total sample and stratified by gender.

Results: Pregabalin was present on 240 (16%) toxicology reports of 1489 poisoning deaths; significantly rising from 18 (5%) in 2013 to 94 (27%) in 2016. Women (AOR 2.69, 95% CI: 1.95-3.70), opioid misuse (AOR 1.74, 95% CI: 1.17-2.59), in receipt of treatment for problem drug use (AOR 1.95, 95% CI: 1.33-2.86) and year of death (2016 vs 2013) (AOR 7.95, 95% CI: 4.58-13.79) were associated with increased odds of PPPD. Alcohol dependence was associated with reduced odds of PPPD (AOR 0.59, 95% CI: 0.41-0.85). For men, opioid misuse, in receipt of treatment for problem drug use, and year of death were associated with increased odds of PPPD, while alcohol dependence was associated with reduced odds of PPPD. For women, in receipt of treatment for problem drug use and year of death were associated with increased odds of PPPD.

Conclusions: Enhanced training to prescribers and treatment providers on the potential risks associated with pregabalin, particularly among people who use drugs, is required.

4.2 Introduction

Pregabalin is a prescribed medication licensed in Europe for use in the treatment of epilepsy, neuropathic pain, and generalized anxiety disorder (European Medicines Agency, 2019; Gajraj, 2007). Pregabalin is also approved in the United States for treating fibromyalgia (Boomershine, 2010). Following its introduction in 2004 in Europe and the United States, rates of prescribing have increased both nationally (Health Service Executive, 2019; Lynn et al., 2019) and internationally (Cairns et al., 2019; Goodman and Brett, 2017; Schwan et al., 2010; Spence, 2013). The increasing numbers of conditions for which pregabalin is indicated for treatment, combined with an increased tendency among clinicians to prescribe pregabalin for these conditions, as has been reported in the United States (Goodman and Brett, 2017), may partly account for the increase in use; however, they are unlikely to fully explain the growth in pregabalin use (Schwan et al., 2010). Off-label prescribing for non-neuropathic pain has increased (Mathieson et al., 2017; Shanthanna et al., 2017), which may be due to prescribers seeking an alternative to opioid analgesics (Goodman and Brett, 2017; Morrison et al., 2017; Schwan et al., 2010).

Pregabalin was initially considered to have low abuse potential (European Medicines Agency, 2006), and although limited, there is some evidence to suggest that pregabalin may be effective in the treatment of withdrawal symptoms linked to dependency, especially in relation to opioids, benzodiazepines and alcohol (Freynhagen et al., 2016). However, the pharmacokinetic properties of pregabalin, which include its rapid absorption, fast onset of its relaxant and sedative effects and its reduced withdrawal symptoms, can lead to the potential risk of misuse (Bonnet and Scherbaum, 2017; Morrison et al., 2017). Several recent studies have reported its misuse; especially among people with a history of opioid misuse (Evoy et al., 2017; Lyndon et al., 2017; United Nations, 2019), people in opioid substitution treatment (Grosshans et al., 2013; McNamara et al., 2015) and people in prisons (Farmer, 2013). Although it requires more investigation, a growing body of evidence suggests that pregabalin may be addictive among people with a history of dependence to other substances (Bonnet et al., 2018; Bonnet and Scherbaum, 2017) and caution should be taken if prescribing to people with a history of opioid dependency (Abrahamsson et al., 2017). Poisoning deaths involving pregabalin almost always involved other drugs, mainly opioids (Cairns et al., 2019; Lyndon et al., 2017; Eastwood and Davison, 2016;

Häkkinen et al., 2014). In 2009, indications that pregabalin may have been involved in deaths in Sweden, Finland and the United Kingdom among people who use drugs were reported to the European Monitoring Centre for Drugs and Drug Addiction (European Monitoring Centre for Drugs and Drug Addiction, 2010a). Current information from the European Medicines Agency (2019) suggests that cases of misuse, abuse, and dependency of pregabalin have been reported and advise monitoring for symptoms of misuse among patients especially individuals with a history of substance abuse. Furthermore, analysis of non-fatal intentional overdoses in Ireland between 2007 and 2015 (*n* = 72,391), based largely on self-reports, supplemented with ambulance records, hospital medical records and toxicology reports, where available, showed an increased presence of gabapentinoids, including pregabalin, especially among women (Daly et al., 2018). While a recent study suggests a possible association between the increase in pregabalin use in Ireland with a corresponding increase in pregabalin-related poisoning deaths (Lynn et al., 2019), in this study we aim to examine factors associated with pregabalin-positive poisoning deaths in Ireland between 2013 and 2016 in order to inform policy and practice to help reduce these deaths.

4.3 Methods

The STROBE checklist (STROBE Statement, 2007) was used as a guide to structure this study report.

4.3.1 Study design, setting and population

This retrospective repeated cross-sectional 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 2013 to 2016 inclusive. The NDRDI is an epidemiological database which records all poisoning deaths by drugs and/or alcohol (Lynn et al., 2009). The NDRDI also records deaths among persons with a recorded history of drug and/or alcohol dependence or non-dependent misuse of drugs irrespective of whether the drug was or was not directly implicated in the death (defined as “non-poisoning”). It must be noted that the NDRDI only records if a person is alcohol dependent when it is clearly documented that the person was alcohol dependent or had a medical condition associated with alcohol dependency such as

alcoholic liver disease. Documentation of phrases such as ‘abused alcohol’ or ‘misused alcohol’ are not sufficient to classified as alcohol dependent.

The NDRDI’s definition of a poisoning death is a death directly due to the toxic effect of one or more substances on the body; for this study pregabalin-positive poisoning deaths (PPPD) included all poisoning deaths where pregabalin was present on the toxicology report. The State Laboratory performs all postmortem toxicology screening in Ireland. From 2013 onwards pregabalin was included in the routine postmortem toxicology screening in the State Laboratory (Y. Kavanagh, personal communication, July 2018), therefore, to ensure completeness of data, the years of death 2013 to 2016 inclusive was selected as the observation period for this study. The study was approved by the Royal College of Surgeons in Ireland Research Ethics Committee on 1st May 2018, reference number; REC 1542.

4.3.2 Data sources

The NDRDI follows the EMCDDA standard protocol to collect data on drug-related deaths which is used in 28 European countries, Norway and Turkey (European Monitoring Centre for Drugs and Drug Addiction, 2010b). To ensure completeness, data from several sources are collected and cross-checked to avoid duplication. Coronial files are the main data source and include postmortem toxicology reports where required for death investigation. All toxicological analyses included in this study were performed by the State Laboratory in Ireland. Other NDRDI data sources include the General Register Office via the Central Statistics Office, acute hospitals data (via the Hospital In-patient Enquiry System [HIPE]) and the national opioid substitution treatment register (the Central Treatment List [CTL]). Further details on the NDRDI methodology can be found elsewhere (Lynn et al., 2009).

4.3.3 Study variables

The primary outcome was pregabalin-positive poisoning deaths (PPPD) which refers to all poisoning deaths with pregabalin present on toxicology reports, for the years of death 2013 to 2016 inclusive. The comparison group was all other poisoning deaths, referred to as pregabalin-negative poisoning deaths (PNPD). Poisoning deaths included all deaths with ICD-10 Version 2004 codes; X40-49 (accidental), X60-69 (intentional) or Y10-19 (undetermined intent) (World Health Organisation, 2004).

NDRDI drug codes were assigned to specific drugs present on toxicology reports and up to ten drugs were recorded for each death.

Potential factors included in this study from available data collected by the NDRDI were based on scientific evidence on poisoning deaths. We included data on gender, age at death, socioeconomic factors such as unemployment and homelessness (Rönkä et al., 2017), and whether a person was alone at the time of the incident that lead to the death (Lynn et al., 2018). Other potential factors included were specifically related to PPPD; alcohol dependency (Bonnet and Scherbaum, 2017), opioid misuse (Abrahamsson et al., 2017; Lyndon et al., 2017), being in receipt of treatment for problematic drug use, particularly methadone substitution treatment (Grosshans et al., 2013; McNamara et al., 2015) and the presence of polydrugs on toxicology reports, especially other central nervous system (CNS) depressant drugs such as opioids, benzodiazepines and alcohol (Eastwood and Davison, 2016; Häkkinen et al., 2014). Due to the legal requirement for Coroners in the Irish system to establish 'beyond reasonable doubt' that a death was a suicide, as opposed to 'based on the balance of probability', suicide deaths are likely to be under-estimated (Corcoran and Arensman, 2010), therefore detailed analysis on the manner of death, beyond descriptive statistics, was not included.

4.3.4 Statistical analysis

The primary outcome of interest was PPPD. Correlations between covariates were calculated to assess for any collinearity. Due to a strong collinearity between opioids and benzodiazepines recorded on toxicology reports, a new variable; number of other CNS depressant drugs on toxicology report, was computed. This new variable included alcohol.

An adjusted logistic regression model included all factors found to be significant at $p<0.10$ in the unadjusted analyses (age; gender; year of death; alone at time of incident that led to death; unemployed; homeless; alcohol dependent; opioid misuse; in receipt of treatment for problematic drug use). Odds ratios (OR) and 95% confidence intervals (CI) were reported for both the unadjusted and adjusted models. Interactions were assessed between gender and other covariates (year of death; age group; alone at time of incident that led to death; unemployment; homeless; alcohol dependent; opioid misuse; in receipt of treatment for problematic drug use) included in the adjusted model to determine whether stratification by gender was appropriate.

Table 4.1 Factors associated with PPPD, 2013 to 2016 (n=1489)

			All poisoning deaths		Men	Women
			Unadjusted model	Adjusted model	Adjusted model	Adjusted model
Factors *(reference category)*	PNPD	PPPD	Odds ratio (95% CI)	Odds ratio (95% CI)	Odds ratio (95% CI)	Odds ratio (95% CI)
Gender						
Women	356	111 (24%)	2.16 (1.63-2.86)***	2.69 (1.95-3.70)***		
Men(ref)	893	129 (13%)	1.00	1.00		
Year of death						
2013 (ref)	382	18 (5%)	1.00	1.00	1.00	1.00
2014	317	53 (14%)	3.33 (2.04-6.18)***	3.62 (2.04-6.42)***	4.46 (2.00-10.05)***	2.74 (1.18-6.34)*
2015	290	75 (21%)	5.49 (3.21-9.39)***	5.55 (3.20-9.66)***	5.14 (2.28-11.56)***	6.05 (2.76-13.26)***
2016	260	94 (27%)	7.67 (4.52-13.01)***	7.95 (4.58-13.79)***	11.01 (5.02-24.14)***	5.24 (2.35-11.69)***
Age groups						
Age group ≤34yrs (ref)	389	73 (16%)	1.00	1.00	1.00	1.00
Age group 35-44yrs	357	95 (21%)	1.42 (1.01-1.99)*	1.12 (0.77-1.63)	1.22 (0.76-1.96)	0.97 (0.51-1.87)
Age group 45-54yrs	237	43 (15%)	0.97 (0.64-1.46)	1.02 (0.64-1.63)	1.09 (0.59-2.03)`	0.91 (0.43-1.93)
Age group ≥55yrs	266	29 (10%)	0.58 (0.37-0.92)*	0.70 (0.41-1.21)	0.54 (0.22-1.34)	0.82 (0.38-1.73)
Alone at time of incident that led to death						
Yes	578	99 (15%)	0.78 (0.59-1.04)	0.93 (0.67-1.28	0.72 (0.47-1.09)	1.30 (0.78-2.18)
No(ref)	578	127 (18%)	1.00	1.00	1.00	1.00
Unknown	93	14 (13%)	0.69 (0.38-1.24)	1.0 (0.50-2.00)	0.83 (0.31-2.21)	1.23 (0.44-3.48)
Unemployed						
Yes	612	151 (20%)	1.72 (1.24-2.39)**	1.31 (0.87-1.95)	0.97 (0.56-1.68)	1.76 (0.98-3.18)
No(ref)	405	58 (13%)	1.00	1.00	1.00	1.00
Unknown	232	31 (12%)	0.93 (0.59-1.49)	0.87 (0.52-1.45)	0.57 (0.28-1.16)	1.49 (0.70-3.19)
Homeless						
Yes	130	36 (22%)	1.44 (0.97-2.15)	0.94 (0.59-1.49)	1.08 (0.62-1.88)	0.84 (0.35-2.05)
No(ref)	1017	195 (16%)	1.00	1.00	1.00	1.00
Unknown	102	9 (8%)	0.46 (0.23-0.93)	0.61 (0.28-1.30)	1.11 (0.44-2.77)	0.21 (0.05-0.97)
History of alcohol dependency						
Yes	360	48 (12%)	0.62 (0.44-0.87)**	0.59 (0.41-0.85)**	0.45 (0.27-0.76)**	0.84 (0.48-1.47)
No(ref)	889	192 (18%)	1.00	1.00	1.00	1.00
History of opioid misuse						
Yes	553	160 (22%)	2.52 (1.88-3.37)***	1.74 (1.17-2.59)**	1.83 (1.09-3.08)*	1.56 (0.81-3.01)
No(ref)	696	80 (10%)	1.00	1.00	1.00	1.00
In receipt of treatment for problematic drug use						
Yes	197	89 (31%)	3.15 (2.32-4.26)***	1.95 (1.33-2.86)**	1.80 (1.10-2.95)*	2.57 (1.31-5.01)**
No(ref)	1052	151 (13%)	1.00	1.00	1.00	1.00

Adjusted model is for all predictors identified as significant in the unadjusted models. Variables significant at *** p<0.001, ** p<0.01, * p<0.05

Table 4.2 Main other drugs on toxicology reports associated with PPPD, with unadjusted odds ratios for men and women presented separately, 2013 to 2016 (n=1489)

	All poisoning deaths 2013-2016			Men	Women
Main other drugs present on toxicology reports *(reference category)*	PNPD	PPPD	Unadjusted odds ratio (95% CI)	Unadjusted odds ratio (95% CI)	Unadjusted odds ratio (95% CI)
Polydrugs present on toxicology reports					
Yes	1042	240 (19%)			
No	207	0			
Breakdown of other CNS depressant drugs on toxicology					
Opioids *(ref: none)*	658	211 (24%)	6.54 (4.36-9.79)***	5.04 (2.98-8.54)***	11.07 (5.87-20.89)***
Methadone *(ref: none)*	287	122 (30%)	3.47 (2.61-4.61)***	3.27 (2.24-4.76)***	4.40 (2.78-6.96)***
Heroin *(ref: none)*	298	44 (13%)	0.72 (0.50-1.02)	0.81 (0.53-1.23)	1.11 (0.54-2.29)
Benzodiazepines *(ref: none)*	669	207 (24%)	5.44 (3.71-7.98)***	5.49 (3.24-9.30)***	5.68 (3.21-10.03)***
Alcohol *(ref: none)*	653	58 (8%)	0.29 (0.21-0.40)***	0.30 (0.20-0.45)***	0.30 (0.18-0.49)***
Number of other CNS depressant drugs on toxicology report					
One	468	29 (6%)	1.88 (0.77-4.60)	1.37 (0.44-4.20)	3.09 (0.68-13.96)
Two or more	599	205 (25%)	10.38 (4.53-23.77)***	6.85 (2.47-18.95)***	23.23 (5.56-97.13)***
None (ref)	182	6 (3%)			
Antidepressants on toxicology report					
Yes	429	178 (29%)	5.49 (4.02-7.49)***	4.92 (3.32-7.30)***	5.24 (3.07-8.95)***
No (ref)	820	62 (7%)			
Z drugs on toxicology report					
Yes	318	116 (27%)	2.74 (2.06-3.64)***	2.79 (1.91-4.08)***	2.33 (1.51-3.60)***
No (ref)	931	124 (12%)			
Antipsychotics on toxicology report					
Yes	194	99 (34%)	3.82 (2.83-5.15)***	3.57 (2.39-5.35)***	3.67 (2.32-5.80)***
No (ref)	1055	141 (12%)			
Cocaine on toxicology report					
Yes	174	34 (16%)	1.02 (0.69-1.52)	1.04 (0.63-1.69)	1.54 (0.75-3.16)
No (ref)	1075	206 (16%)			

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

Significant collinearity was observed between other drugs present on toxicology reports and ‘a history of opioid misuse’ and ‘in receipt of treatment for problematic drug use’ (Appendix 4.1 Supplementary Table D) therefore we did not include the presence of other drugs in the adjusted model. The association between other drugs on toxicology reports and PPPD are reported separately. Data were analysed using SPSS version 22.

4.4 Results

4.4.1 Description of study population

A total of 1489 poisoning deaths were recorded by the NDRDI between 2013 and 2016, of which 240 (16%) were identified as PPPD. While the total number of poisoning deaths appeared to decrease over the four years, there was an increase in PPPD, rising from 18 deaths (2013) to 94 deaths (2016) (Table 4.1). The median age was similar for both PNPD (41 years (interquartile range (IQR) 18) and PPPD (40 years (IQR 13)). In this sample, 240 (19%) of PNPD and 50 (21%) of PPPD had no formal verdict recorded, therefore, detailed analysis beyond reporting these percentages of suicide deaths by sex was not included. A similar percentage of men from both the PPPD (11, 8.5%) and PNPD (78, 8.7%) groups had a verdict of suicide recorded. A slightly higher percentage of women in the PNPD group (45, 12.6%) had a verdict of suicide recorded compared to women in the PPPD group (12, 10.8%).

4.4.2 Factors associated with PPPD

After adjustment for significant covariates: gender, year of death, history of opioid misuse and in receipt of treatment for problem drug use, were all associated with an increase in PPPD (Table 4.1). Relative to men, women were almost three times more likely to experience a PPPD (AOR 2.69, 95% CI 1.95-3.70, p=<0.001). More recent poisoning deaths were significantly more likely to be PPPD, for example poisoning deaths in 2016 were almost 8 times more likely to be PPPD relative to 2013 (AOR 7.67, 95% CI 4.52-13.01, p=<0.001). Those with a history of opioid misuse, or in receipt of treatment for problematic drug use were almost twice as likely to have a PPPD. In contrast, alcohol dependence was associated with reduced odds of PPPD (Table 4.1). Being alone at the time of the incident that led to the deaths or being

homeless were not found to be significantly associated with PPPD. In univariate analysis, being unemployed and age were associated with increased odds of PPPD however in the adjusted model this association did not remain independently significant.

4.4.3 Gender specific analysis

The following gender by covariate interactions were found to be statistically significant at $p < 0.05$: year of death, unemployment, homeless, history of opioid misuse, and in receipt of treatment for problematic drug use. Similar to the overall analysis: year of death, history of opioid misuse and being in receipt of treatment for problem drug use were all independently associated with an increase in PPPD for men, with history of alcohol dependence associated with reduced odds of PPPD for men. Year of death and being in receipt of treatment for problem drug use were the only covariates associated with an increase in PPPD for women (Table 4.1).

4.4.4 Toxicology

Polydrugs were present on the toxicology reports of all PPPD (n=240). Almost all (234, 97.5%) had a positive toxicology report for other CNS depressant drugs, mainly opioids (211, 88%), followed by benzodiazepines (207, 86%) and alcohol (58, 24%) (Table 4.2). Methadone (122, 51%) was the main opioid reported in PPPD, followed by heroin (44, 18%). The odds of opioid drugs being present on toxicology reports (versus none) was 6.54 times more likely for PPPD than PNPD (Table 4.2) with the odds for women twice that for men.

Significant collinearity was observed between a history of opioid misuse and the covariates: number of other CNS depressant drugs on toxicology ($r = 0.49$, $p < 0.01$), antipsychotics on toxicology ($r = -0.16$, $p < 0.05$) and cocaine on toxicology ($r = -0.31$, $p < 0.01$) (Appendix 4.1: Supplementary Table D). Significant collinearity was also observed between being in receipt of treatment for problematic drug use and the covariates: number of other CNS depressant drugs ($r = 0.29$, $p < 0.01$) and cocaine on toxicology ($r = -0.28$, $p < 0.01$) (Appendix 4.1: Supplementary Table D). These findings lead to the decision to analyse toxicology results separately.

Two or more other CNS depressant drugs were present in the majority (205, 85%) of PPPD toxicology reports (Table 4.2). The odds of two or more CNS depressant drugs being present on toxicology reports (versus none) was 10.38 times

more likely for PPPD compared to PNPD (Table 4.2) with the odds for women three times that for men.

The odds of antidepressant drugs present on toxicology (versus none) was 5.49 times more likely for PPPD than PNPD; for antipsychotic drugs the odds ratio was 3.82; and for z drugs 2.74 (Table 4.2). The presence of cocaine on toxicology reports was not statistically significantly associated with PPPD (Table 4.2).

4.5 Discussion

4.5.1 Summary of findings in context of previous studies

In this national study of poisoning deaths in Ireland, we found that despite an observed reduction in overall poisoning deaths between 2013 and 2016, there was a significant increase in PPPD over the same period for both men and women. Almost one in six poisoning deaths were PPPD, with women at a higher risk of PPPD relative to men. This finding is consistent with previous studies which identified a high prevalence of pregabalin use among women and an associated elevated risk of PPPD among women (Cairns et al., 2019; Daly et al., 2018; McNamara et al., 2015). Pregabalin is licensed to treat generalized anxiety disorder, which is more common among women (Albert, 2015; Craske and Stein, 2016), therefore this may contribute partly to more pregabalin use among women. During the study period there was a decrease in both poisoning deaths involving diazepam (Health Research Board, 2019b) and in the dispensing frequency of diazepam (Health Service Executive, 2019), with a corresponding rise in both poisoning deaths involving pregabalin and in the dispensing frequency of pregabalin (Lynn et al., 2019). This may suggest a change in prescription practices in the treatment of generalized anxiety disorder in Ireland. International studies have also demonstrated an increase in the prescribing of pregabalin (Cairns et al., 2019; Goodman and Brett, 2017).

Having two or more other CNS depressant drugs, antidepressants, antipsychotics and/or z drugs on toxicology were significantly associated with PPPD. As previously stated, evidence shows that poisoning deaths involving pregabalin almost always involved other drugs, mainly opioids; however, the very high level of other CNS depressant drugs present in PPPD, especially among women, found in our study is of concern. Women have a high incidence of polydrug use; therefore, their

risk of a poisoning death is more substantial (Origer et al., 2014). This is evident in our study where women are over-represented in PPPD and women who died of PPPD were three times more likely than men to have two or more other CNS depressant drugs present on toxicology. Pregabalin can exacerbate the side effects of CNS depressant drugs (European Medicines Agency, 2019) and with multiple CNS drugs present in PPPD, the synergistic effect of the combination of these drugs increasing the risk of death. Taking these factors into account and the upward trend reported in polydrug poisoning deaths in Ireland (Health Research Board, 2019b), the findings from our study suggest that pregabalin has contributed to this increase in polydrug poisoning deaths.

The odds of having antidepressants and/or antipsychotic drugs present on toxicology was higher for PPPD then PNPD. The high reliance on pharmaceutical treatment for mental illnesses, especially among people with dual diagnoses of mental illness and addiction, highlights the need for more diverse treatment options including more focus on psychological treatment. This will require more resources in the treatment setting but may save lives by preventing the cumulative side effects of combinations of CNS depressant drugs such as benzodiazepines, opioids and pregabalin.

A positive history of alcohol dependence has been reported among people who misuse gabapentinoids (Bonnet and Scherbaum, 2017), however in our study, alcohol dependence was not found to be associated with PPPD among women but was associated with reduced odds of PPPD among men. Despite this result, alcohol does play a significant role in PPPD in our study given that almost a quarter of PPPD also had alcohol, a CNS depressant, present in their system at the time of death and it is known that pregabalin exacerbates the side effects of CNS depressant drugs (European Medicines Agency, 2019). Of note, the strict threshold for inclusion of alcohol dependence in the NDRDI may underestimate the true figure for alcohol dependence in this sample.

In a study by Häkkinen et al. (2014) all PPPD occurred in age groups under 50 years of age, however our study did not find any specific age group to be associated with PPPD, in fact the lowest number of PPPD were in the age group 55 years or older. Being unemployed has been associated with drug-related deaths (Rönkä et al., 2017), yet, although the majority in the PPPD were unemployed, with a higher

proportion of PPPD then PNPD unemployed, unemployment was not associated with PPPD in our study.

4.5.2 Implications for treatment and prescribing practices

In our study, opioid misuse was not associated with PPPD among women, however it was associated with elevated odds for PPPD among men, supporting previous studies in this area (Abrahamsson et al., 2017; Evoy et al., 2017; Lyndon et al., 2017). This suggests that prescribers of pregabalin may not be aware of the potential of abuse for people, especially men, who misuse opioids;- and/or users, including those who may be using pregabalin illegitimately, may not be aware of the potential exacerbation of side effects when pregabalin is taken with other CNS depressants such as opioids.

Being in receipt of treatment for problematic drug use, especially methadone opioid substitution has been associated with a reduced risk of death (Cousins et al., 2016). However, evidence from our study showed that being in receipt of treatment, which mainly consisted of methadone opioid substitution treatment, was a significant factor for PPPD, especially for women. Despite women representing the minority in receipt of treatment for problematic drug use not only in Ireland (Health Research Board, 2019a) but also in Europe (European Monitoring Centre for Drugs and Drug Addiction, 2019), women in receipt of treatment for problematic drug use, were over-represented in the PPPD group. This may suggest a lack of awareness of physiological gender differences affecting drug activity (Whitley and Lindsey, 2009). Pharmacokinetics in women results in slower renal clearance of certain drugs including pregabalin (Whitley and Lindsey, 2009). For women, benzodiazepines are seen to have a longer duration of action and in relation to pharmadynamics, women have greater sensitivity to, and enhanced effectiveness of opioids thus can experience higher levels of respiratory depression from opioids (Algren et al., 2013; Whitley and Lindsey, 2009). Considering these factors, the combination of drugs involved in PPPD may have contributed to the overrepresentation of women in PPPD.

Physicians considering prescribing pregabalin to individuals with problematic drug use must carefully balance the potential benefits with the risk of misuse or dependency, especially when used in combination with other drugs (Schifano, 2014). In addition to advice from the European Medicines Agency (2019), research suggests that for those with problematic drug use, gabapentinoid drugs, which includes

pregabalin, should be avoided and if prescribed, must be accompanied with strict therapeutic and prescription monitoring (Bonnet and Scherbaum, 2017; Ponton, 2018).

Prescribers may require further advice and training, as an initial step, to ensure prescribing practices are appropriate. Furthermore, increased emphasis including resources, on the provision of psychological treatment may decrease reliance on pharmaceutical treatment.

4.5.3 Policy and legislation

A strong correlation was reported between the increase in PPPD and the increased number of dispensing's of pregabalin in Ireland from 2013 to 2016 (Lynn et al., 2019). In the United States the increased pregabalin use has been related to 'off label' use as an alternative to opioids for various pain management (Goodman and Brett, 2017). While exploratory evidence suggests benefits in the treatment of pain management, there has been no confirmatory evidence to support this (Carlisle et al., 2018), therefore, more restrictions on 'off label' use should be considered.

From April 2019, following recommendations from the Advisory Council on the Misuse of Drugs, pregabalin (and gabapentin) was classified as a class C drug in the United Kingdom. This means that pregabalin cannot be repeat-dispensed and prescriptions are valid for just one month. Despite acknowledgement that this incurs extra work for doctors, pharmacists and especially patients; the medical profession supported this change (Torjesen, 2019). Similar reclassification should be considered in Ireland.

A national ePrescription system, as proposed by national and European experts (Clark et al., 2015; Health Information and Quality Authority, 2015; Health Service Executive, 2013), would assist in preventing people altering prescriptions or receiving multiple private prescriptions, especially multiple CNS depressant drugs, from different medical practitioners.

4.5.4 Strengths and limitations

This is the first study to comprehensively examine the profile of poisoning deaths involving pregabalin in Ireland during the period 2013 to 2016, made possible by using the NDRDI data. The availability of toxicology reports that can be linked to circumstances surrounding the death provides a unique opportunity to

comprehensively analyse these deaths. The differences in risk factors identified by gender highlights the importance of including gender stratified analysis in reporting data on drug-related deaths. Findings from this study add to existing evidence on risk factors for PPPD but also provide new evidence in relation to specific risk factors by gender and the profile of PPPD in Ireland. Limitations of this study include the reliance on the information available from data sources which were not primarily collected for research purposes. This can lead to under-reporting of some data and other data not routinely collected. For example, data is not always available on the source of the drug (illicit or licit) or the reason for prescribing pregabalin. The sample size was a complete sample of PPPD in Ireland but was limited to 129 men and 111 women. Furthermore, lack of complete data on formal verdicts did not facilitate analysis by verdict. Another limitation is the lack of comparison data on living persons using pregabalin.

4.5.5 Future research

NDRDI data reported a decrease in heroin-related poisoning deaths annually since 2014 with a rise in pregabalin-related poisoning deaths over the same period (Health Research Board, 2019b), which could relate to findings by Lyndon et al. (2017) suggesting that some people who use heroin believe pregabalin has similar effects, therefore pregabalin may be replacing some heroin use (Lyndon et al., 2017). This is an area that requires further investigation, including the possibility of using pregabalin under strict medical monitoring, to assist in treating withdrawal symptoms associated with drug dependence including opioids, benzodiazepines and alcohol (Freynhagen et al., 2016).

4.5.6 Conclusion

PPPD are increasing in line with the increasing use of pregabalin. Findings from our study suggest inappropriate use of pregabalin among those who are known to misuse opioids and those in receipt of treatment for problematic drug use. More guidance and training for prescribers and treatment providers and the development of policies, including consideration given to scheduling pregabalin as a controlled drug, is recommended to better inform the public and medical practitioners of the potential harm due to ‘off label’ prescribing and of inappropriate use of pregabalin.

Close monitoring of prescribing practices, diversion, and misuse of pregabalin, especially among those who use opioids and within the treatment setting in Ireland is

urgently required. Any treatment with pregabalin should be subject to regular review with caution adhered to when considering prescribing pregabalin to women who are taking other drugs, especially CNS depressants. In Ireland, the nationwide implementation of an ePrescription system would assist in this process.

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Chapter 5: Comparing characteristics of suicide to non-suicide drug poisoning deaths, by sex, in Ireland

This chapter is based on the paper: Comparing characteristics of suicide to non-suicide drug poisoning deaths, by sex, in Ireland. Published March 2022 in the Journal of Affective Disorders.

Study aim

The aim of this study is to determine the extent to which individual and social contextual factors, and specific drugs/drug groups influence risk of suicide compared to non-suicide drug poisoning deaths, and to determine whether there are differences between men and women in a national Irish study of drug poisoning deaths between 2015 and 2017.

Sex specific analysis

The following sex by covariate interactions were found to be statistically significant at $p < 0.05$: ever incarcerated, chronic pain, previous overdose, and CNS depressant drugs implicated in the death.

Sensitivity analysis (Appendix 5.2)

In the sensitivity analysis only the legal definition of suicide (as documented by the coroner on the record of verdict) was used in the analysis. Results from the sensitivity analysis were similar to the study analysis, however due to low numbers, some variables may not have met the level of significance seen in the main study.

Author contributions

EL, KB and GC designed the study. EL was responsible for the writing of the manuscript and undertook the statistical analysis with guidance from KB and GC. All authors provided critical input to drafts of the paper. All authors contributed to the interpretation of the data and approved the final manuscript.

5.1 Abstract

Background: Suicide by drug poisoning is potentially preventable; however, evidence on associated risk factors by sex is limited.

Aim: To assist in understanding how individual and social contextual factors, and specific drugs, influence risk of suicide compared to non-suicide drug poisoning deaths, and how this differs by sex.

Methods: Data were extracted from the National Drug-Related Deaths Index. Analysis included univariable and multivariable logistic regression to estimate unadjusted and adjusted odds ratios (OR) and 95% confidence intervals (CI) for factors associated with suicide drug poisoning deaths (SDPD) (primary outcome) compared with non-suicide drug poisoning deaths (NSDPD) and stratified by sex.

Results: SDPD accounted for 240 (22%) of 1114 poisoning deaths, the majority among men (n = 147, 61%). Increasing age, mental ill health (AOR 7.85, 95% CI: 5.46-11.28), chronic pain (AOR 5.57, 95% CI: 3.28-9.46), and history of previous overdose (AOR 5.06, 95% CI: 3.39-7.56) were associated with increased odds of SDPD, with similar results for both sexes. The main drugs associated with SDPD were non-opioid analgesics (OR 4.06 [95% CI 2.66 – 6.18]), antipsychotics (OR 2.42 [95% CI 1.63 – 3.60]) and antidepressants (OR 2.18 [95% CI 1.59 – 2.97]). Pregabalin was associated with SDPD among women only.

Limitations: Secondary analysis of coronial data on drug poisoning deaths therefore findings may not be relevant to suicide deaths in general.

Conclusions: Ongoing monitoring for signs of suicidal intent in individuals with mental illness, chronic pain, overdose, and/or prescribed mental health medications may identify individuals in need of additional intervention.

5.2 Background

Suicide is a significant public health concern with over 700,000 people worldwide dying by suicide each year. Accurate data on suicide deaths, including the characteristics of those who die by suicide and factors associated with these deaths, is essential to inform effective suicide prevention strategies (World Health Organisation, 2014). Factors that contribute to all suicide deaths are complex, wide-ranging, and multi-faceted (Hawton and van Heeringen, 2009). In the United States drug poisonings are estimated to account for 8.4% of suicides among men and 31% of suicides among women (Petrosky et al., 2020). In Europe drug poisonings are estimated to account for 9.1% of suicides among young men and 23% of suicides among young women (Värnik et al., 2008). However, despite the prevalence of suicide by drug poisoning, a preventable method of suicide, (Värnik et al., 2011) there is a lack of research on this topic, including the specific drug groups involved in these deaths (Miller et al., 2020).

Furthermore, a recent scoping review identified the lack of data on suicide drug poisoning deaths, stratified by sex, as an important gap in the literature (Lynn et al., 2020a). Absence of sex-stratified mortality data can mask important sex-based differences in mortality trends (Masters et al., 2017). The majority of all drug poisoning deaths are among men, and most of these deaths are classified as unintentional (Olfson et al., 2019; Austin et al., 2017). Therefore, data related to drug poisoning deaths among men, and unintentional drug poisoning deaths tend to dominate research evidence.

A scoping project in Scotland reported that suicides account for a greater proportion of drug poisoning deaths among women relative to men (Tweed et al., 2018). It also found that women who use drugs are more likely than their male peers to have concurrent mental health problems (Tweed et al., 2018), a risk factor for suicide (Roxburgh et al., 2015).

An observational study of suicide drug poisoning deaths (SDPD) in New Mexico (United States) between 2008-2012, found the majority of SDPD (62%) were among women, with women being significantly more likely to have multiple drugs present at the time of death compared to men (Szymanski et al., 2016). Almost three quarters (73%) of people identified as dying from SDPD were identified as having a psychiatric illness, most frequently depression (87%). Chronic pain was reported in 27% of cases,

and decedents with chronic pain were primarily women (68%) (Szymanski et al., 2016). A 2012 study in North Carolina (United States) also identified a higher prevalence of SDPD among women (64%) relative to men (36%), with older age associated with SDPD compared to non-suicide drug poisoning deaths (NSDPD). Antidepressants were also identified as contributing to SDPD compared to NSDPD (Austin et al., 2017). However, more recent data from the United States indicates the rate of SDPD is now higher among men relative to women (Centers for Disease Control and Prevention, 2021). A recent Irish study examining fatal and non-fatal intentional drug poisonings during the period 2007 to 2014 reported that men, increasing age, polydrug use, tricyclic antidepressants (TCAs) and opioids were associated with increased risk of SDPD. The risk of death following an intentional overdose was 1.7 times greater for men compared to women; however, women had higher rates of antipsychotics and TCAs implicated in the suicide death relative to men (Daly et al., 2020).

To identify specific factors associated with suicide drug poisoning deaths, it is important to examine factors associated with suicide drug poisoning stratified by sex, including assessment of risk by drug group (Miller et al., 2020). This will help provide essential information to understand the scope of the problem so that interventions can be tailored to meet the requirements, and influence public health policy to help decrease these preventable deaths (World Health Organisation, 2019; Kumpula et al., 2017; Sinyor et al., 2012).

Study Aim

To determine the extent to which individual and social contextual factors, and specific drugs/drug groups are associated with suicide compared to non-suicide drug poisoning deaths, and to determine whether there are differences between men and women in a national Irish study of drug poisoning deaths between 2015 and 2017.

5.3 Methods

5.3.1 Study design

This population based observational study used the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist (von Elm et

al., 2008) in reporting the study. The study was approved by the Royal College of Surgeons in Ireland Research Ethics Committee on 1st May 2018, reference number; REC 1542.

5.3.2 Data source and population

National Drug-Related Deaths Index (NDRDI)

This study includes anonymized individual level data on all drug poisoning deaths in Ireland as recorded by the NDRDI for years of death 2015 to 2017 inclusive. The NDRDI is an epidemiological database, managed by the Health Research Board in Ireland, which records all poisoning deaths by drugs and/or alcohol (Lynn et al., 2009). 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 and/or the record of verdict. All drugs implicated in drug poisoning deaths, as recorded by the coroner, are included in the NDRDI. However, the primary drug implicated in drug poisoning deaths is not routinely identified. The NDRDI also follows the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) standard protocol to collect data on drug-related deaths which is used in European countries, Norway and Turkey (EMCDDA, 2010). To ensure completeness, data from several sources are collected and cross-checked to avoid duplication. NDRDI data sources include: national coronial records, the General Mortality Register (Central Statistics Office (CSO)), acute hospitals data (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 (Lynn et al., 2009; Lynn et al., 2020b).

Study population

The study population comprised of deaths which met the NDRDI criteria for drug poisoning deaths for the years of death 2015 to 2017 inclusive. The years 2015-2017 were chosen as the classification of suicide deaths based on the balance of probabilities was introduced for 2015 deaths, and 2017 is the latest complete year of data available from the NDRDI. The SDPD group includes all drug poisoning deaths that met both the narrow ('beyond reasonable doubt') as recorded by the coroner, and broad ('based on the balance of probabilities') definitions of suicide. Suicide based on the balance of probabilities was identified using the Rosenberg criteria for

determination of suicide (Rosenberg et al., 1988). To be included 'based on the balance of probabilities' the death had to be self-inflicted and there had to be evidence of intent to die in addition to risk factors for suicide. Deaths within this category may have received an undetermined or accidental verdict by the coroner but using the Rosenberg criteria and based on the evidence available in the coronial file they were included in the broader classification of suicide. Deaths which received an undetermined or accidental verdict by the coroner and did not meet the broader inclusion criteria for SDPD were included in the NSDPD category. Further details of the death investigation process and methodology used to determine suicide 'based on the balance of probabilities' is included in the supplementary document (Appendix 5.3).

Outcome

The primary outcome is suicide drug poisoning deaths (SDPD), and was compared to all other drug poisoning deaths, referred to as non-suicide drug poisoning deaths (NSDPD).

5.3.3 Study variables

Poisoning deaths include all deaths with ICD-10 Version 2004 codes: X40-49 (accidental), X60-69 (intentional) or Y10-19 (undetermined intent) (World Health Organisation, 2004). NDRDI drug codes are assigned to specific drugs linked to the ICD codes. Up to six individual drugs implicated in the death can be recorded by the NDRDI for each individual death, therefore multi-response analysis was carried out.

Drug groups and individual drugs included

Analysis included the main drug groups, and individual drugs involved in drug poisoning deaths during the study period, including: opioids (T40.2, T40.3, T40.4 & T40.6), benzodiazepines (T42.4), alcohol (T51), antidepressants (T43.0 & T43.2), antipsychotic drugs (T42.1. T42.6, T43.3, T43.4 & T43.5, with specific drug codes for individual drugs identified), Z drugs (zolpidem / zopiclone, T42.6), non-opioid analgesics (T30.0, T30.1, T39.3 & T39.9), cocaine (T40.5) and heroin (T40.1).

Evidence suggests a link between TCAs (Daly et al., 2020; Hawton et al., 2010) and intentional drug poisoning deaths; therefore, antidepressant drugs implicated in the deaths were recoded into three categories of antidepressants: selective serotonin

reuptake inhibitors (SSRIs), TCAs and other antidepressants. SSRI group ATC codes included: N06AB04 (citalopram), N06AB03 (fluoxetine), N06AB10 (escitalopram), N06AB06 (sertraline) and N06AB05 (paroxetine). TCA group ATC codes included: N06AA09 (amitriptyline), N06AA16 (dosulepin), N06AA06 (trimipramine), N06AA04 (clomipramine), N06AA10 (nortriptyline), N06AA01 (imipramine) and N06AA12 (doxipen). Other antidepressants group included: N06AX16 (venlafaxine), N06AX21 (duloxetine), N06AX11(mirtazapine), N06AX05 (trazodone) and N06AF04 (tranylcypromine).

Drug poisoning deaths involving any opioids, benzodiazepines, alcohol, pregabalin, and/or Z drugs were aggregated into a new variable 'CNS depressant drugs'. The same category was included in a recent trends analysis of drug poisoning deaths in Ireland (Lynn et al., 2021). A separate variable was computed to identify if the death involved a combination of two or more CNS depressant drugs.

Risk factors

Potential risk factors for SDPD and/or suicide in general were included based on previous study findings: sex (Daly et al., 2020; Szymanski et al., 2016; Barnsdale et al., 2018), age at death (Curtin et al., 2017; Miller et al., 2020; Lynn et al., 2020a), marital status (single [including separated or divorced] or other status) (Sinyor et al., 2012) especially among men (Corcoran and Nagar, 2010), alcohol dependence (Ferrari et al., 2014) especially among women (Bohnert et al., 2017), socioeconomic factors such as unemployment (Rönkä et al., 2017) and homelessness (Bauer et al., 2016; Office for National Statistics, 2020). Being homeless was defined as no fixed abode, including temporary insecure living arrangements.

We included other potential factors associated with drug poisoning deaths such as: illicit drug use (Hesse et al., 2020; Ferrari et al., 2014; Lynch et al., 2020), alcohol dependency (Bonnet and Scherbaum, 2017; Bohnert et al., 2017), not in receipt of treatment for substance use disorder (Cousins et al., 2016; Durand et al., 2020; Hesse et al., 2020), history of incarceration (Haglund et al., 2014; Spittal et al., 2014; Viner et al., 2018), history of previous overdose (Rossow and Lauritzen, 1999), mental health issues as reported by medical professionals and/or in depositions taken as part of the death investigation (Roxburgh et al., 2015; Lynch et al., 2020), chronic pain (Hooley et al., 2014; Cheatle, 2011), and single (Sinyor et al., 2012) or polydrug (Szymanski et al., 2016) involvement.

Other covariates

Age was recoded from continuous age according to the following categories: ≤34, 35-44, 45-54 and ≥55 years. Sex is included in the overall analysis of factors associated with SDPD. Analysis are also stratified by sex for comparison.

5.3.4 Statistical analysis

The primary outcome of interest is SDPD. Descriptive analyses including frequencies, proportions, medians (inter-quartile range [IQR]) and 95% confidence intervals are presented. Correlations between covariates are examined to assess for collinearity prior to inclusion in the adjusted logistic regression model. Analyses are presented overall and stratified by sex.

We adjusted for the following clinically relevant covariates: alcohol dependency and single marital status. Sex, age, unemployed, homeless, single marital status, previous incarceration, history of drug use, alcohol dependent, history of previous overdose, in receipt of treatment for substance use disorder, and history of mental health issue(s) were considered for inclusion in the multivariable analysis based on the p-value from the univariable analysis ($p<0.10$) or importance as suggested by previously published evidence. In the overall models including sex as a variable, men are the reference category; the youngest age group is the reference category for age; and the outcome ‘no’ is the reference category for the remaining covariates. Unadjusted and adjusted odds ratios (OR) and 95% confidence intervals (CI) are reported for both the unadjusted and final adjusted models respectively.

Although history of drug use was found to be significant in the univariable analysis, significant collinearity was observed between this covariate and the following covariates: in receipt of treatment for substance use disorder, previous incarceration, and age groups; therefore, ‘history of drug use’ was excluded from the adjusted multivariable logistic regression model.

Due to strong collinearity between the various drugs/drug groups and other covariates (i.e., previous incarceration, history of alcohol dependence, in receipt of treatment for substance use disorder, history of chronic pain, and mention of mental ill health), separate logistic regression models were applied to each of the different drugs/drug groups implicated in the deaths, with analysis presented overall and stratified by sex. Unadjusted OR and 95% CIs are presented. Data were analysed

using SPSS version 22 (IBM SPSS Statistics for Windows, v.22.0. Armonk, NY: IBM Corp.). Significance at $p<0.05$ is assumed; however, significant associations at $p<0.05$, $p<0.01$ and $p<0.001$ are displayed in the tables of results.

5.4 Results

5.4.1 Description of study population

A total of 1,114 drug poisoning deaths were recorded on the NDRDI between 2015 and 2017. Over one fifth (n = 240, 22%) of these deaths were classified as SDPD. The majority of SDPD (n = 147, 61%) and NSDPD (n = 608, 70%) were among men. However, a higher proportion of women (n = 93, 26%) relative to men (147, 19%) who died of drug poisoning, died of SDPD (Table 5.1).

For all drug poisoning deaths, the median age was higher for women (46 years (IQR 22 [37 – 59]) relative to men (41 years (IQR 17 [33 – 50])) (p = <0.01). Relative to all drug poisoning deaths, the median age was higher, for both sexes, for SDPD (women: 49 years (IQR 21 [40 – 61]), men: 47 years (IQR 18 [38 – 56])) with no statistically significant difference between the sexes. Deaths within the NSDPD group had a lower median age relative to SDPD, with the median age difference between the sexes statistically significant (p = <0.001) (women: 44.5 years (IQR 23 [35 – 58]), men: 40 years (IQR 17 [32 – 49])). The difference between age at death in the SDPD group compared to NSDPD was statistically significant (p = <0.001).

Men accounted for the majority (n = 473, 72%) of drug poisoning deaths among people with a history of drug use (n = 657). The majority of drug poisoning deaths among people with a history of drug use were NSDPD (n = 587, 89%).

Factors associated with SDPD

After adjusting for covariates in the multivariable logistic regression model; age, mental illness, chronic pain, and a history of previous overdose, were all associated with SDPD (Table 5.1). Those with mental ill health were seven times more likely to die of SDPD than NSDPD. Those with a history of chronic pain or a previous overdose were approximately five times more likely to die of SDPD compared to NSDPD (Table 5.1).

Women were less likely to die of SDPD relative to men (Table 5.1). Unemployment, previous incarceration, in receipt of treatment for substance use disorder, and alcohol dependency were all associated with reduced odds of SDPD compared to NSDPD.

5.4.2 Analysis stratified by sex

Following adjustment, for women: the younger age group (35-44 years of age), the oldest age group (≥55 years of age), mental ill health, chronic pain and history of a previous overdose were independently associated with increased odds of SDPD, with a history of incarceration independently associated with reduced odds of SDPD compared to NSDPD (Table 5.2).

Similar results, with small variations in magnitude of effects, were observed for men in relation to the older age, mental ill health, chronic pain, history of a previous overdose and history of incarceration. In addition, for men: being unemployed, alcohol dependent, and being in receipt of treatment for substance use disorder were all independently associated with reduced odds of SDPD compared to NSDPD (Table 5.2). The reference groups used for this analysis included deaths among the youngest age group (≤34yrs), people with no history of mental ill health, and/or chronic pain, and/or a previous overdose.

No association was found between homeless status and SDPD for either men or women in the adjusted model (data is not presented in the table due to the small number of deaths).

Table 5.1 Unadjusted and adjusted ORs (95% CI) comparing characteristics and factors for suicide drug poisoning deaths (SDPD) [n=240] versus non-suicide drug poisoning deaths (NSDPD) [n=874], NDRDI data 2015 to 2017 inclusive [n=1114]

	SDPD (% of total deaths	NSDPD	Unadjusted model	Adjusted model†
Sex				
Women	93 (26%)	266	1.45 (1.08 - 1.95)*	0.62 (0.42 - 0.91)*
Men (Ref)	147 (20%)	608	1.00	1.00
Age group				
≤34yrs(Ref)	31 (11%)	252	1.00	1.00
35-44yrs	67 (19%)	281	1.94 (1.23 - 3.07)**	2.09 (1.20 - 3.65)**
45-54yrs	63 (27%)	173	2.96 (1.85 - 4.74)***	2.36 (1.31 - 4.22)**
≥55yrs	79 (32%)	168	3.82 (2.42 - 6.05)***	3.01 (1.68 - 5.38)***
Mention of mental ill health				
Yes	199 (37%)	334	7.85 (5.46 - 11.28)***	7.03 (4.67 - 10.58)***
No(Ref)	41 (7%)	540	1.00	1.00
History of chronic pain				
Yes	35 (57%)	26	5.57 (3.28 - 9.46)***	4.54 (2.39 - 8.62)***
No(Ref)	205 (20%)	848	1.00	1.00
Known history of previous overdose				
Yes	60 (53%)	54	5.06 (3.39 - 7.56)***	4.54 (2.72 - 7.59)***
No(Ref)	180 (18%)	820	1.00	1.00
Previous incarceration				
Yes	26 (7%)	349	0.18 (0.12 - 0.28)***	0.34 (0.20 - 0.57)***
No(Ref)	214 (29%)	525	1.00	1.00
In receipt of treatment for substance use disorder				
Yes	21 (9%)	211	0.30 (0.19 - 0.48)***	0.41 (0.23 - 0.73)**
No(Ref)	219 (25%)	663	1.00	1.00
History of alcohol dependency				
Yes	55 (17%)	270	0.67 (0.48 - 0.93)*	0.46 (0.30 - 0.69)***
No(Ref)	185 (23%)	604	1.00	1.00
Unemployed				
Yes	76 (14%)	466	0.35 (0.25 - 0.48)***	0.63 (0.41 - 0.98)*
No(Ref)	118 (32%)	251	1.00	1.00
Employment status unknown	46 (23%)	157	0.62 (0.42 - 0.93)	1.13 (0.69 - 1.86)
Homeless Status				
Homeless	9 (7%)	113	0.26 (0.13 - 0.53)***	0.59 (0.26 - 1.34)
Not homeless(Ref)	231 (23%)	761	1.00	1.00
Single marital status (includes separated/divorced)				
Yes	163 (21%)	608	0.67 (0.48 - 0.93)*	1.03 (0.69 - 1.56)
No(Ref)	70 (29%)	175	1.00	1.00
Marital status unknown	7 (7%)	91	0.19 (0.09 - 0.44)	0.26 (0.10 - 0.68)

Significant associations at * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$
†Adjusted model includes all variables

5.4.3 Drugs implicated in the deaths

The reference group for this analysis was deaths which did not have the specific drug/drug group implicated in the death. A similar percentage of SDPD (60%) and NSDPD (61%) had polydrugs implicated in the deaths.

5.4.3.1 Drugs associated with increased odds of SDPD

Non-opioid analgesics

Non-opioid analgesics were associated with and increased odds of SDPD, (OR 4.06 [95% CI 2.66 – 6.18]) overall, and for both men and women. Although, the magnitude of this effect was greater among women (Table 5.3). Paracetamol (n = 43, 88%) was the main non-opioid analgesic within this drug group involved in SDPD. Just over half (n = 22, 51%) of SDPD involving paracetamol also involved a codeine-based drug.

Anti-depressant drugs

Antidepressant drugs were also significantly more likely to be implicated in SDPD (OR 2.18 [95% CI 1.59 – 2.97]). This effect appears to be driven by TCAs for both men and women (Table 5.3). Amitriptyline was the main TCA drug implicated in these deaths (n = 24, 73%). Of the 24 SDPD involving amitriptyline, all had a history of mental illness, with eight (25%) having a history of mental illness and comorbid chronic pain.

Antipsychotic drugs

Antipsychotic drugs were also associated with SDPD overall (OR 2.42 [95% CI 1.63 – 3.60]), and among both men and women, with the magnitude of the effect greater among women (Table 5.3). Quetiapine was the main antipsychotic drug implicated in SDPD (n = 22) with the majority among women (n = 17, 77%). Olanzapine was the second most common antipsychotic drug involved in SDPD (n = 16) with a slightly higher percentage among women (n = 9, 56%).

Z-drugs and pregabalin

Z-drugs were significantly more likely to be implicated in SDPD (OR 1.43 [95% CI 1.00 – 2.03]). However, these effects did not remain in the sex-specific analyses. In contrast, pregabalin was associated with SDPD among women only (Table 5.3). Of

the 28 deaths among women where pregabalin was implicated in the cause of death, it is known that 89% (n = 25) had a history of mental health illness and two fifths (n = 9) of these women also had a history of chronic pain.

Table 5.2 Unadjusted and adjusted ORs (95% CI) comparing characteristics and factors for suicide drug poisoning deaths (SDPD) [n=240] versus non-suicide drug poisoning deaths (NSDPD) [n=874], stratified by sex, NDRDI data 2015 to 2017 inclusive [n=1114]

	Drug poisoning deaths among men				Drug poisoning deaths among women			
	SDPD n (% of total)	NSDPD n	Unadjusted model	Adjusted model	SDPD n (% of total)	NSDPD n	Unadjusted model	Adjusted model
Age group								
≤34yrs(Ref)	23 (11%)	192	1.00	1.00	8 (12%)	60	1.00	1.00
35-44yrs	38 (15%)	208	1.53 (0.88 - 2.65)	1.58 (0.81 - 3.08)	29 (28%)	73	2.98 (1.27 - 7.00)*	3.52 (1.17 - 10.56)*
45-54yrs	44 (27%)	122	3.01 (1.73 - 5.23)***	2.64 (1.33 - 5.21)*	19 (27%)	51	2.79 (1.13 - 6.92)*	2.03 (0.63 - 6.58)
≥55yrs	42 (33%)	86	4.08 (2.31 - 7.20)***	3.19 (1.57 - 6.48)*	37 (31%)	82	3.38 (1.47 - 7.79)**	3.13 (1.02 - 9.55)*
Mention of mental ill health								
Yes	115 (36%)	204	7.12 (4.65 - 10.90)***	7.54 (4.64 - 12.23)***	84 (39%)	130	9.76 (4.71 - 20.23)***	7.19 (3.19 - 16.20)***
No(Ref)	32 (7%)	404	1.00	1.00	9 (6%)	136	1.00	1.00
History of chronic pain								
Yes	13 (48%)	14	4.12 (1.89 - 8.96)***	2.73 (1.05 - 7.10)*	22 (65%)	12	6.56 (3.10 - 13.90)	6.75 (2.72 - 16.72)***
No(Ref)	134 (18%)	594	1.00	1.00	71 (22%)	254	1.00	1.00
Known history of previous overdose								
Yes	28 (44%)	36	3.74 (2.20 - 6.34)***	4.25 (2.11 - 8.56)***	32 (64%)	18	7.23 (3.80 - 13.73)***	5.46 (2.44 - 12.21)***
No(Ref)	119 (17%)	572	1.00	1.00	61 (20%)	248	1.00	1.00
Ever incarcerated								
Yes	18 (6%)	281	0.16 (0.10 - 0.27)***	0.31 (0.16 - 0.58)***	8 (11%)	68	0.27 (0.13 - 0.60)**	0.46 (0.16 - 1.31)**
No(Ref)	129 (28%)	327	1.00	1.00	85 (30%)	198	1.00	1.00
In receipt of treatment for substance use disorder								
Yes	10 (7%)	138	0.25 (0.13 - 0.49)***	0.32 (0.15 - 0.70)**	11 (13%)	73	0.36 (0.18 - 0.70)	0.41 (0.15 - 1.13)
No(Ref)	137 (23%)	470	1.00	1.00	82 (30%)	193	1.00	
History of alcohol dependency								
Yes	31 (15%)	183	0.62 (0.40 -0.96)*	0.40 (0.24 - 0.68)**	24 (22%)	87	0.72 (0.42 - 1.22)	0.55 (0.28 - 1.07)

No(Ref)	116 (21%)	425	1.00	1.00	69 (28%)	179	1.00	
Unemployed								
Yes	51 (13%)	348	0.33 (0.21 - 0.49)***	0.57 (0.33 - 0.98)*	25 (18%)	118	0.43 (0.25 - 0.74)**	0.87 (0.41 - 1.85)
No(Ref)	65 (21%)	144	1.00	1.00	53 (33%)	107	1.00	1.00
Employment status unknown	31 (21%)	116	0.59 (0.36 - 0.97)	1.07 (0.57 - 2.01)	15 (27%)	41	0.74 (0.38 - 1.45)	1.25 (0.53 - 2.99)
Single marital status								
Yes	102 (19%)	440	0.57 (0.38 - 0.88)*	0.77 (0.45 - 1.30)	61 (27%)	168	0.91 (0.54 - 1.54)	1.40 (0.72 - 2.75)
No(Ref)	41 (29%)	102	1.00	1.00	29 (28%)	73	1.00	
Marital status unknown	4 (6%)	66	0.15 (0.05 - 0.44)	0.19 (0.06 - 0.63)*	3 (11%)	25	0.30 (0.09 - 1.08)	0.40 (0.07 - 2.18)

Significant associations at * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

Table 5.3 Unadjusted ORs (95% CI) of drugs implicated in drug poisoning deaths (suicide drug poisoning deaths (SDPD) [n=240] verses non-suicide drug poisoning deaths [n=874] (NSDPD)), overall and stratified by sex, NDRDI data 2015 to 2017 inclusive [n=1114]

	All drug poisoning deaths			Drug poisoning deaths among men			Drug poisoning deaths among women		
	SDPD N=240	NSDPD N=874	Unadjusted model	SDPD N=147 (19%)	NSDPD N=608 (81%)	Unadjusted model	SDPD N=93 (26%)	NSDPD N=266 (74%)	Unadjusted model
CNS depressants implicated in poisoning death (% of deaths within each drug poisoning death group)									
Yes	137 (57%)	779 (89%)	0.16 (0.12 - 0.23)***	73 (50%)	543 (89%)	0.12 (0.08 - 0.18)***	64 (69%)	236 (89%)	0.28 (0.16 - 0.50)***
No (Ref)	103 (43%)	95 (11%)	1.00	74 (50%)	65 (11%)	1.00	29 (31%)	30 (11%)	1.00
Two or more other CNS depressant drugs									
Yes	92 (38%)	473 (54%)	0.53 (0.39 - 0.71)***	44 (30%)	330 (54%)	0.36 (0.24 - 0.53)***	48 (52%)	143 (54%)	0.92 (0.57 - 1.47)
No (Ref)	148 (62%)	401 (46%)	1.00	103 (70%)	278 (46%)	1.00	45 (48%)	123 (46%)	1.00
Breakdown of CNS depressant drugs									
Prescription opioids implicated in poisoning death									
Yes	82 (34%)	376 (43%)	0.69 (0.51 - 0.93)*	39 (27%)	246 (40%)	0.53 (0.36 - 0.79)**	43 (46%)	130 (49%)	0.90 (0.56 - 1.44)
No (Ref)	158 (66%)	498 (57%)	1.00	108 (73%)	362 (60%)	1.00	50 (54%)	136 (51%)	1.00
Benzodiazepines implicated in poisoning death									
Yes	63 (26%)	373 (43%)	0.48 (0.35 - 0.66)***	35 (24%)	257 (42%)	0.43 (0.28 - 0.65)***	28 (30%)	116 (44%)	0.56 (0.34 - 0.92)*
No (Ref)	177 (74%)	501 (57%)	1.00	112 (76%)	351 (58%)	1.00	65 (70%)	150 (56%)	
Z-drugs implicated in poisoning death									
Yes	52 (22%)	145 (17%)	1.43 (1.00 - 2.03)*	27 (18%)	83 (14%)	1.42 (0.88 - 2.29)	25 (27%)	62 (23%)	1.28 (0.75 - 2.18)
No (Ref)	188 (78%)	729 (83%)	1.00	120 (82%)	525 (86%)	1.00	68 (73%)	204 (77%)	1.00
Pregabalin implicated in poisoning death									
Yes	41 (17%)	117 (13%)	1.33 (0.90 - 1.97)	13 (9%)	67 (11%)	0.78 (0.42 - 1.46)	28 (30%)	50 (19%)	1.86 (1.09 - 3.19)*
No (Ref)	199 (83%)	757 (87%)	1.00	134 (91%)	541 (89%)	1.00	65 (70%)	216 (81%)	1.00
Heroin implicated in poisoning death									
Yes	9 (4%)	226 (26%)	0.11 (0.06 - 0.22)***	6 (4%)	193 (32%)	0.09 (0.04 - 0.21)***	3 (3%)	33 (12%)	0.24 (0.07 - 0.79)*
No (Ref)	231 (96%)	648 (74%)	1.00	141 (96%)	415 (68%)	1.00	90 (97%)	233 (88%)	1.00
Alcohol implicated in poisoning death									
Yes	37 (15%)	339 (39%)	0.29 (0.20 - 0.42)***	25 (17%)	236 (39%)	0.32 (0.20 - 0.51)***	12 (13%)	103 (39%)	0.23 (0.12 - 0.45)***
No (Ref)	203 (85%)	535 (61%)	1.00	122 (83%)	372 (61%)	1.00	81 (87%)	163 (61%)	1.00
Main other drugs implicated in poisoning death									
Antidepressants									
Yes	85 (35%)	176 (20%)	2.18 (1.59 - 2.97)***	40 (27%)	89 (15%)	2.18 (1.42 - 3.34)***	45 (48%)	87 (33%)	1.93 (1.19 - 3.12)**
No (Ref)	155 (65%)	698 (80%)	1.00	107 (73%)	519 (85%)	1.00	48 (52%)	179 (67%)	1.00
Type of antidepressant drugs[Y]									

SSRIs									
Yes	33 (14%)	77 (9%)	1.65 (1.07 - 2.55)*	15 (10%)	36 (6%)	1.81 (0.96 - 3.40)	18 (18%)	41 (15%)	1.32 (0.71 - 2.43)
No (Ref)	207 (86%)	797 (91%)	1.00	132 (90%)	572 (94%)	1.00	75 (81%)	225 (85%)	1.00
TCAs									
Yes	33 (14%)	43 (5%)	3.08 (1.91 - 4.97)***	16 (11%)	22 (4%)	3.25 (1.66 - 6.37)**	17 (18%)	21 (8%)	2.61 (1.31 - 5.20)**
No (Ref)	207 (86%)	831 (95%)	1.00	131 (89%)	586 (96%)	1.00	76 (82%)	245 (92%)	1.00
Other antidepressants									
Yes	40 (17%)	96 (11%)	1.62 (1.09 - 2.42)*	19 (13%)	50 (8%)	1.66 (0.94 - 2.91)	21 (23%)	46 (17%)	1.40 (0.78 - 2.49)
No (Ref)	200 (83%)	778 (89%)	1.00	128 (87%)	558 (92%)	1.00	72 (77%)	220 (83%)	1.00
Antipsychotics									
Yes	46 (19%)	78 (9%)	2.42 (1.63 - 3.60)***	21 (14%)	47 (8%)	1.99 (1.15 - 3.45)*	25 (27%)	31 (12%)	2.79 (1.54 - 5.04)**
No (Ref)	194 (81%)	796 (91%)	1.00	126 (86%)	561 (92%)	1.00	68 (73%)	235 (88%)	1.00
Non opioid analgesics									
Yes	49 (20%)	53 (6%)	4.06 (2.66 - 6.18)***	25 (17%)	34 (6%)	3.57 (2.05 - 6.22)***	24 (26%)	19 (7%)	4.52 (2.34 - 8.73)***
No (Ref)	191 (80%)	821 (94%)	1.00	122 (83%)	574 (94%)	1.00	69 (74%)	247 (93%)	1.00
Cocaine									
Yes	12 (5%)	129 (15%)	0.30 (0.17 - 0.56)***	8 (5%)	97 (16%)	0.30 (0.14 - 0.64)**	˜ (4%)	32 (12%)	0.33 (0.11 - 0.96)*
No (Ref)	228 (95%)	745 (85%)	1.00	139 (95%)	511 (84%)	1.00	89 (96%)	234 (88%)	1.00

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

¥ Individuals may have more than one antidepressant drugs implicated in their death therefore total figures from each antidepressant drug group category may not equal to the total number of individual deaths involving antidepressants

˜ field contains value less than 5

5.5 Discussion

5.5.1 Summary of findings in the context of previous studies

Factors associated with SDPD included being male, older age, mental illness, chronic pain, and history of a previous overdose. The main drugs found to be associated with SDPD included non-opioid analgesics, antidepressants (specifically TCAs), and antipsychotics. Similar effects were observed among men and women in the sex-specific analyses, with small variations in magnitude of effects.

Individual and social contextual factors

Men account for the majority of all suicides in Ireland (Health Service Executive, 2020); therefore, men accounting for the majority of SDPD is not unexpected, and is similar to recent statistics from the United States showing a higher age-adjusted rate of SDPD among men at 1.9 per 100,000 compared to 1.7 per 100,000 among women (Centers for Disease Control and Prevention, 2021). However, this may suggest a variation in means of suicide by sex, which warrants further investigation, as previous reports from a European-wide study, (Värnik et al., 2008) and from the United States (Szymanski et al., 2016; Austin et al., 2017) using older data, reported a higher percentage of women relative to men used drug poisoning as a method of suicide.

Despite men accounting for the majority of all SDPD, we found that SDPD contributed to a higher proportion of overall drug poisoning deaths among women relative to men. This finding supports results from a Scottish mixed-methods study showing SDPD account for a greater percentage of drug-related deaths among women than men (Tweed et al., 2020).

Similar to previous studies in the United States (Austin et al., 2017) and Switzerland (Pfeifer et al., 2020), we observed a higher median age at time of SDPD for both men and women.

A retrospective review of SDPD in the United States showed an association between having a history of mental ill health and overall SDPD (Szymanski et al., 2016). Our findings, where deaths among people with no history of mental ill health was the reference group, suggest mental ill health is a significant risk factor for SDPD relative to NSDPD, for men and for women. The key objectives of ‘The European Mental Health Action Plan’, such as ensuring mental health services are

accessible and affordable, and provide respectful, safe, and effective treatment, should be resourced (World Health Organization, 2021). However, mental illness-related stigma can be a barrier to accessing effective treatment (World Health Organization, 2021). Evidence from a systematic review and meta-analysis suggest all types of contact and education interventions are effective in reducing stigma towards people with mental illness in the short-term and should be implemented more widely (Morgan et al., 2018).

Daly et al. (2020), in estimating case fatality risk associated with intentional drug overdose, reported the risk of SDPD (using the narrow, legal suicide verdict), to be higher for men relative to women. Our study, which included both the narrow legal and the broader 'based on the balance of probabilities' definitions of suicide but did not differentiate between a history of intentional or unintentional drug overdose, also found a strong association between having a history of a previous overdose, relative to no documented history of a previous overdose, and SDPD. However, similar to findings by Sinyor et al. (2012) we found the odds for this association to be stronger for women relative to men. This finding supports a recommendation from a systematic review on the association between a history of non-fatal self-harm and suicide; that all people presenting with non-fatal self-harm should be routinely assessed for suicide risk (Witt et al., 2019). Given the risk of suicide following any self-harm, the provision of early follow-up care, which includes risk reduction strategies (Geulayov et al., 2019), is recommended. Effective pharmacological and psychological treatments are central in preventing suicide (Zalsman et al., 2016). However, as recommended by Daly et al. (2020), clinicians should consider the case fatality risk of drugs when prescribing pharmacological treatment for people who have a history of a previous intentional drug overdose.

In line with our findings, studies examining drug poisoning of all manners of death (Barnsdale et al., 2018), drug poisoning deaths among women (United Nations, 2018; United States, 2017) and suicide drug poisoning deaths (Szymanski et al., 2016), identified chronic pain as an associated risk factor in these deaths, especially for women. When prescribing pain medication, screening for mental illness and suicide risk is appropriate (Sinyor et al., 2012). More research on optimal treatment for chronic pain and broader inclusion of non-pharmaceutical treatment in pain management should be explored.

Being in receipt of treatment for substance use disorder is associated with lower rates of all causes of mortality (Cousins et al., 2016; Degenhardt et al., 2011; Santo et al., 2021). While our study does not include all causes of mortality, being in receipt of treatment for substance use disorder relative to not being in receipt of treatment, was associated with decreased odds for SDPD among men. We know that men account for the majority of people in receipt of treatment for substance use disorder (EMCDDA, 2020); therefore, more effort to decrease barriers to and retain people, especially women, in treatment is required. This finding is likely to have particular relevance to other countries, such as Northern European countries, who have similar drug use profiles to Ireland.

A retrospective cohort study in the United States examining risk factors for NSDPD following release from prison, reported that previously incarcerated individuals are at high risk of NSDPD, especially in the early weeks post release (Viner et al., 2018). While history of incarceration was found to be associated with decreased odds of SDPD relative to NSDPD, a specific time period post release is not included in our study and the potential risk of NSDPD, especially within the initial period post release remains.

Case-control and cohort studies in the United States found an increased risk of suicide for both men and women with a history of substance use disorder, including alcohol dependency (Lynch et al., 2020; Hesse et al., 2020; Bohnert et al., 2017). Our study found, compared to people with no history of alcohol dependency, having a history of alcohol dependency was associated with decreased odds of SDPD relative to NSDPD but only for men. However, as our study focuses on SDPD, findings pertaining to specific factors may not be relevant to suicide deaths in general.

Unemployment was identified as a factor associated with all drug-related deaths in Finland (Rönkä et al., 2017). While our study, looking specifically at SDPD, found unemployment was associated with decreased odds of SDPD for men, this must be interpreted with caution as a high number of deaths where the employment status of the deceased was unknown may be a confounding factor in the outcome for this covariant.

5.5.2 Drugs implicated in the deaths

The main drugs associated with SDPD were non-opioid analgesics, antidepressants, especially TCAs, and antipsychotics. Decreased prescriptions of barbiturates and TCAs have been shown to reduce suicide by drug poisoning (Sarchiapone et al., 2011). Limited pack size for non-opioid analgesics, in addition to a minimum 18-years of age purchase restriction have been shown to reduce overdoses with these drugs (Morthorst et al., 2020). These findings are consistent with an earlier systematic review on suicide prevention strategies, which reported a decrease in suicides related to restrictions on the prescription and sale of barbiturates, changing packaging of analgesics to blister packets and use of new, lower toxic antidepressants (Mann et al., 2005).

Suicidal acts can be impulsive and therefore facilitated by easily accessible drugs such as over-the-counter non-opioid analgesics. Research findings from Ireland, the UK (Hawton et al., 2011) and Denmark (Morthorst et al., 2020) confirm that more restrictive measures in accessing non-opioid analgesics, including limiting package size, and number of items sold in one transaction, are associated with a reduction in related poisonings. However, an individual in Ireland can still purchase numerous products by attending several outlets; a minimum 18-years of age purchase restriction is not in place in Ireland; and non-opioid analgesics such as paracetamol continue to be implicated in drug poisoning deaths, albeit most often in combination with other drugs. In Ireland, up to 24 paracetamol units can be purchased in one transaction from a pharmacy, while only up to 12 paracetamol units can be purchased in one transaction from non-pharmacy outlets, with different regulations depending on the strength of the individual dose (Government of Ireland, 2003). Given the potential to breach these regulations (Mhaoláin et al., 2007), consideration should be given to decrease the number of units permitted to be dispensed as an over-the-counter item from a pharmacy in line with regulations for sale through non-pharmacy outlets.

While a systematic review examining the effectiveness of suicide prevention interventions concluded that antidepressant pharmacotherapy treatment is associated with reduced suicide risk (Zalsman et al., 2016), the association we found between antidepressants and SDPD concurs with previous literature (Barnsdale, 2018; Austin et al., 2017; Miller et al., 2020). A review of literature on controlling access to means of suicide suggests an association with increased prescribing of

less toxic SSRI antidepressants and a reduction in overall suicide rates (Sarchiapone et al., 2011). The association between antidepressants and SDPD in this study appears to be driven by TCAs. While our study only focuses on drug poisoning deaths, results contribute to a growing body of research which highlights the association between SDPD and use of TCAs (Pfeifer et al., 2020; Daly et al., 2020; Hawton et al., 2010). Similar to results from a Canadian study (Sinyor et al., 2012), the main TCA drug implicated in SDPD was amitriptyline. Giving the annual increase in the number of amitriptyline products dispensed during the same time period, through the Irish Health Service Executive (Health Service Executive, 2021), and the greater risk of suicidal thoughts or suicide attempts among people who have a prior history of suicide-related issues (Health Products Regulatory Authority, 2019), it is important for prescribers to provide careful monitoring during treatment and consider the potential toxicity of TCAs being used as a means of suicide.

A UK study assessing the toxicity of mood stabilisers and antipsychotic drugs, using case fatality and fatal toxicity associated with intentional poisoning, found clozapine to be more toxic than quetiapine or olanzapine (Ferrey et al., 2018). In our study the main antipsychotic drug implicated in SDPD was quetiapine, with over three quarters of these deaths among women. Meta-analyses have found clozapine to demonstrate anti-suicidal effects among people with schizophrenia (Asenjo Lobos et al., 2010), but also found quetiapine to show no specific effects on the occurrence of suicide when compared to other antipsychotic drugs (Suttajit et al., 2013). Additional stricter dispensing regulations for clozapine in Ireland compared to the UK (Nielsen et al., 2016) could be a potential contributing factor to lower numbers of SDPD involving clozapine in Ireland. Quetiapine was the main antipsychotic drug dispensed through the Irish Primary Care Reimbursement Service (PCRS) during the study observation period, with the majority dispensed to women (PCRS, personal communication, August 31, 2020). More guidelines on dispensing of, and increased monitoring for signs of risk of self-harm among people in receipt of antipsychotic drugs is warranted.

Pregabalin was associated with SDPD among women only. Given the high prevalence of pregabalin use among women who die of drug poisoning deaths (Lynn et al., 2020b; Cairns et al., 2019) and that pregabalin use has been found to be associated with an increased risk of suicidal behaviour (Molero et al., 2019), caution should be applied when prescribing pregabalin, especially to women.

While CNS depressant drugs were found to be associated with decreased odds of SDPD, the prevalence of these drugs in drug poisoning deaths (Lynn et al., 2021) warrants the need to highlight the dangers of the synergistic effect of taking multiple CNS depressant drugs to prevent NSDPD.

5.5.3 Policy and practice implications

Results from this study have important implications for prevention and intervention strategies intended to address SDPD. The association of antidepressant and antipsychotic drugs with SDPD is a strong indication that the deceased may have been in contact with medical services around the time of death. Examining characteristics of SDPD in the United States, SDPD decedents were more likely than NSDPD decedents to have had a prescription within 30 days of their death, indicating contact with the health care system and the potential opportunity to assess the person's mental health status within weeks of their death (Austin et al., 2017).

Psychiatric disorders are a risk factor for suicidal behaviour, and appropriate pharmacological treatment for such disorders assists in preventing suicide (Zalsman et al., 2016). Our findings confirm previous literature, highlighting the association between TCAs and SDPD. Some antidepressants, such as TCAs, are also licenced to treat neuropathic pain; therefore, increased vigilance, including suicide risk assessments, need to be ongoing among people prescribed medication for pain management and people prescribed antidepressants and/or antipsychotics. An appropriate balance reached between the therapeutic effects of drugs and the risk of potential harm from drugs must be met. Patients and their family members should be informed by prescribers of the dangers associated with the toxic effect of drugs. Review of clinical guidelines and indications for use of pregabalin, especially for women, may be required.

Increased resources in the provision of treatment for mental ill health is required. While the benefits of pharmaceutical therapy are unquestionable, more resources for, and incorporation of non-pharmaceutical therapy for mental ill health should be provided. WHO recently highlighted the critical need for mental health services to broaden the provision of treatment beyond pharmaceuticals (World Health Organisation, 2021). WHO recommends a more holistic, person-centred

approach to mental health treatment, which would include psychosocial, psychological and peer support interventions (World Health Organisation, 2021).

5.5.4 Strengths and limitations

The strength of the study is the inclusion of SDPD based on the balance of probabilities in addition to those with the legal verdict of suicide. This provides a more representative and accurate profile of SDPD. Another strength of this study is the use of national data validated from a number of sources, ensuring accuracy and completeness of data available on drug poisoning deaths.

However, there are a number of limitations. Only suicide data on drug poisonings was included in this analysis, therefore, findings pertaining to specific factors may not be relevant to suicide deaths in general. In addition, this study includes data on deceased persons only, therefore future work is required to determine if associations found in this study related to the living general population.

The association between drugs implicated in the deaths and SDPD are unadjusted; therefore, they may under or over-estimate the independent effects of drugs implicated as they lack appropriate adjustment. Our study was unable to assess the impact of non-medical use of prescription drugs; this requires further investigation, given that most of the drugs implicated are prescription drugs. Linking NDRDI data to prescription data would enhance information in this area.

This study is based on secondary analysis of existing coronial data which is collected for investigation of the death and not for research purposes, and so information that is of interest for research may not always be available. Use of coronial data is susceptible to biases such as nonresponse bias and recall bias; therefore, there may have been missing or unknown information which may have introduced potential bias. For example, a number of entries recorded as ‘unknown’ could potentially have been ‘yes’ or ‘no’ but the evidence was not available in the data sources. The power of some associations may have been low, and the possibility of residual confounding remains; therefore, only associations not causal effects can be inferred.

5.6 Conclusion

In determining the extent to which individual and social contextual factors, and specific drugs/drug groups are associated with SDPD compared to NSDPD, this study broadly found consistent findings in relation to associated factors, with small variation in magnitude of effects, for both men and women. Factors associated with SDPD included men, increasing age, mental illness, chronic pain, and a previous overdose. Drugs associated with SDPD included non-opioid analgesics, antidepressants (especially TCAs), and antipsychotics.

Ongoing monitoring for signs of suicidal intent and risk of self-harm in individuals with a history of mental illness, chronic pain, overdose, and/or prescribed mental health medications is vital and may identify individuals in need of additional intervention.

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Chapter 6: Discussion

The overall aim of this thesis was to explore what is known about poisoning deaths among women, identify gaps in knowledge and contribute to filling this knowledge gap. An important contribution, using the public health approach framework (Centers for Disease Control and Prevention, 2022), was disseminating the evidence-based findings to stakeholders to help influence policy and practice and future research with the aim of preventing premature drug poisoning deaths among women. This current chapter provides a summary of findings in context of previous literature (6.1), followed by a discussion of the strengths and limitations (6.2), research impact (6.3), future research (6.4) and conclusions (6.5).

6.1 Summary of findings

The first objective of this thesis was to investigate the extent of existing knowledge on drug poisoning deaths among women. Chapter 2 presents a scoping review of drug poisoning deaths among women. This scoping review found that most published studies on drug poisoning deaths among women involved epidemiological trends with limited in-depth analysis of factors explaining these trends. Within the studies reviewed, there is a dearth of knowledge exploring the contribution of candidate factors or a combination of these factors on drug poisoning deaths among women. Given the prominence of men in drug poisoning deaths, this deficit of in-depth sex-specific research on drug poisoning deaths may mask potential risk factors for women (Masters et al., 2017). Drugs most commonly associated with drugs poisoning deaths among women were opioids, especially prescription opioids, antidepressants, and benzodiazepines. Among those who died of drug poisoning, women were generally older than men at time of death. Other factors reported to be associated with drug poisoning deaths among women included; mental ill-health, victim of violence, history of incarceration, involved in sex work and barriers specific for women in accessing treatment for substance use dependence.

Given the limited evidence on factors associated with drug poisoning deaths among women, Chapter 3 addressed the second objective of this thesis; to explore trends in drug poisoning deaths in Ireland stratified by sex to help identify specific drugs/drug groups involved in drug poisoning deaths among women in comparison

to men. This study showed that, in Ireland over a fourteen-year period, 2004 to 2017, the age standardised rate (ASR) for all drug poisoning deaths per 100,000 of the general population increased from 6.86 per 100,000 in 2004 to 8.08 per 100,000 in 2017. This increase was mainly driven by increasing deaths among men with an average annual percentage increase of 2.6%. There was no significant trend change in the rate of drug poisoning deaths observed among women over the same period. For men, cocaine followed by benzodiazepines, antidepressants and prescribable opioids had the highest average annual percentage increase. For women, the average annual percentage increases were seen for prescribable drugs, namely antidepressants, benzodiazepines and prescribable opioids. Of note was the similar average annual percentage increase for both men (3.5%) and women (3%) for drug poisoning deaths involving prescribable opioids.

In the USA prescription opioids, especially fentanyl, are the main drugs driving the increase in drug poisoning deaths (Scholl et al., 2019). However, in Ireland, although drug poisoning deaths involving opioids increased, the main opioid involved in these deaths was methadone, with no trend change noted for deaths involving heroin for men or women (Chapter 3) and deaths involving fentanyl remained low (Health Research Board, 2019). This is similar to findings from other European countries where heroin and/or methadone are the main opioids implicated in drug poisoning deaths, and deaths related to fentanyl and fentanyl analogues are low (European Monitoring Centre for Drugs and Drug Addiction, 2021c). One of the main findings from the study on trends in drug poisoning deaths (Chapter 3) was a significant increase in deaths involving two or more CNS depressant drugs among women.

The third objective of the thesis was to explore potential factors associated with emerging drugs in drug poisoning deaths. One of the CNS depressant drugs influencing the more recent increase in overall drug poisoning deaths was pregabalin (Health Research Board, 2019; Lynn et al., 2019). A repeated cross-sectional study examining factors associated with pregabalin-positive poisoning deaths in Ireland, by sex, was undertaken (Chapter 4). Men who misused opioids and died of drug poisoning were almost twice as likely to have pregabalin on toxicology than men who died of drug poisoning but had no history of misusing opioids. Of note, for women, opioid misuse was not found to have a significant association for pregabalin positive poisoning deaths relative to women with no history of opioid misuse. However, this

study found that women who died of drug poisoning deaths and were in OAT were 2.6 times more likely, relative to men, to have pregabalin present on their toxicology. This finding is consistent with a previous study examining the misuse of pregabalin among people attending addiction services in Ireland, which found women to be overrepresented in the pregabalin positive samples (McNamara et al., 2015). A UK study reported findings on postmortem toxicology of other CNS depressant drugs, particularly opioids and benzodiazepines, in addition to pregabalin, increased the probability of a fatal outcome (Eastwood & Davison, 2016). In our study, the odds of two or more CNS depressant drugs being present on toxicology reports (versus none) was over 10 times more likely for pregabalin-positive poisoning deaths compared to pregabalin-negative poisoning deaths, with the odds for women having two or more CNS depressant drugs present, three times that for men. These findings highlight the importance of consideration given to the pharmacokinetic and pharmacodynamic differences in drug activity, especially with CNS drugs, between the sexes.

As outlined in Chapter 1, drug poisoning deaths contribute to a higher percentage of suicide deaths among women relative to men. The fourth objective of this thesis was to explore potential factors associated with suicide drug poisoning deaths among women relative to men (Chapter 5). In terms of suicide drug poisoning deaths, this study found broadly consistent findings for both men and women in relation to associated factors, with a small variation in magnitude of effects. Factors found to be associated with suicide drug poisoning deaths (SDPD) for both men and women corresponded with previous national and international studies, including increasing age (Austin et al., 2017; Pfeifer et al., 2020), mental ill health (Szymanski et al., 2016), chronic pain (United Nations Office on Drugs and Crime, 2018; Szymanski et al., 2016), and history of a previous overdose (Daly et al., 2020). A previous overdose and chronic pain had a stronger association with SDPD than non-suicide drug poisoning deaths among women. The main drugs associated with SDPD were non-opioid analgesics, antipsychotics, and antidepressants, with a stronger association for SDPD found for non-opioid analgesics and antipsychotics for women. Pregabalin was associated only with SDPD among women. The main group of antidepressant drugs found to be associated with SDPD was tricyclic antidepressants, which supports this association reported by other studies (Daly et al., 2020; Pfeifer et al., 2020; Hawton et al., 2010). Pregabalin was associated with

SDPD among women only. Drug poisoning deaths involving ≥2 CNS depressant drugs were found to be associated with decreased odds of the death being a SDPD relative to a NSDPD, but for men only.

This thesis has contributed to the knowledge of drug poisoning deaths among women across four studies. Overall, the results illustrate the importance of stratifying data on drug poisoning deaths by sex to enable potential risk factors for both men and women to be identified. These results also contribute to an evidence base on which to implement changes to policy, practice, and society to reduce these premature, and potentially preventable deaths. Specifically, while multiple CNS depressant drugs were not significantly associated with suicide drug poisoning deaths relative to non-suicide drug poisoning deaths, this thesis provided evidence of a link between the use of multiple CNS depressant drugs and overall drug poisoning deaths among both men and women, with specific CNS depressant drugs such as pregabalin, having a strong association with drug poisoning deaths among women. This emphasises the necessity for more awareness among prescribers and users of multiple CNS depressant drugs, of the potential adverse outcomes, to avoid unintentional death. There is a need for a strong open, respectful, and trusting therapeutic relationship in a safe environment, between service providers and service users so that people are not fearful of disclosing the extent of their drug use. A Norwegian study assessing beliefs about the nature of addiction found differences in the understanding of SUD among addiction treatment professionals and patients with SUD, highlighting the necessity to provide patient-centred care (Vederhus et al., 2016). A trusting, safe and respectful patient-centred care should enable those providing care to tailor their advice and provide appropriate treatment. This is particularly important for women given the pharmacokinetic and pharmacodynamic differences in drug activity between men and women. In addition, appropriate treatment for opioid dependence developed as a result of long-term use of opioids for chronic pain needs to be tailored to the specific needs of this group (Kakko et al., 2018). Finally, the results highlight the need for continued monitoring of trends in drug-poisoning deaths stratified by sex, to inform policy and practice.

6.2 Strengths and limitations

This section outlines the strengths and limitations of this research, which were referred to previously in the chapters pertaining to each paper included in this thesis.

6.2.1 Key strengths

This thesis includes the first scoping review undertaken on drug poisoning deaths among women. A strength of scoping reviews is the inclusion of all publications, including peer-reviewed articles and gray literature such as government reports, which can be relied on to inform policy and practice, as well as consultation with experts in the area. Weekly email alerts from the search engines Embase and PubMed, which were maintained since May 2018 from the search strategy implemented for the scoping review (Chapter 2), did not yield any significantly new findings specifically on factors pertaining to drug poisoning deaths among women. Results from this scoping review highlighted gaps in knowledge, which became the focus of other studies included in this thesis, and my contribution to ongoing studies which are not part of this thesis.

The main strength of this thesis is the use of national data from the NDRDI validated from a number of sources to improve accuracy and completeness of data. The NDRDI is a complete census of drug poisoning deaths in Ireland. The inclusion of NDRDI data on all drug poisoning deaths within the general population, ensures that data is not specific to only one cohort of people, such as people in OAT, but includes all who died of drug poisoning deaths in Ireland. The inclusion of the study period of 2004 to 2017 is a strength of the study as it enables the examination of trends in drug poisoning deaths (Chapter 3) over a longer period of time. Access to prescription data for prescribed benzodiazepines and antidepressants enabled assessment of the relationship between trends in annual age-standardised prescription rates and age-standardised mortality rates for drug poisoning deaths involving these drugs.

The availability of toxicology reports that can be linked to circumstances surrounding the death provided a unique opportunity to comprehensively analyse drug poisoning deaths where pregabalin was present on toxicology (Chapter 4). This is the first study to comprehensively examine the profile of poisoning deaths

involving pregabalin, including specific risk factors, by sex, in Ireland during the period 2013 to 2016, made possible by using the NDRDI data.

Additionally, the inclusion of suicide drug poisoning deaths (SDPD) based on the balance of probabilities in addition to those with the legal verdict of suicide (Chapter 5) provided, for the first time in Ireland, a more representative and accurate profile of these deaths by sex. In Ireland, whether someone has died by suicide is a legal decision made by a coroner and includes the criteria that the deceased intended to kill themselves and the intention was proved beyond reasonable doubt. Due to the restrictive legally binding nature of official verdicts, it is acknowledged that suicide deaths in Ireland and other countries may be underreported (Corcoran & Arensman, 2010; Tøllefsen et al., 2015). Given the nature of drug poisoning deaths, the added factor that the deceased may be intoxicated by drugs at the time of death adds further to the legal 'doubt' that the deceased intentionally took their own life. The inclusion of SDPD based on the balance of probabilities and given that the process of inclusion was validated by experts in the area of suicide is a significant strength of this study and provides more accurate data for effective suicide prevention strategies.

While associations, and not causation, can be inferred from studies included in this thesis, results may inform the hypotheses to examine in future research.

6.2.2 Key limitations

While using the methodology of a scoping review is appropriate to investigate the extent of existing knowledge on drug poisoning deaths among women, a limitation to scoping reviews is the lack of in-depth quality appraisal of the evidence. The search was limited to publications in the past twenty-one years (1998-2019); therefore, it is possible that potentially relevant publications before 1998 could have been missed. However, literature from before 1998 may not have been as relevant. For example, a systematic review of literature on the topic of non-medical use of prescription drugs found that, although no date limitations were applied, most of the literature dated after 2000 (Clark et al., 2015).

Where publications identified in the scoping review included statistical analysis, they mainly consisted of descriptive, unadjusted statistical analysis. Only five publications selected used multivariable modelling to identify sex-specific differences related to poisoning deaths. Five of the primary studies contained a small

sample size of women compared to the sample size of men, thus limiting their power to investigate specific factors pertaining to drug poisoning deaths among women (Chapter 2). One of the items included was a conference abstract (Iwanicki et al., 2015). This conference abstract was also published in the high-ranking journal; Drug and Alcohol Dependence. The study findings outlined in this abstract, highlighted the overrepresentation of women in drug poisoning deaths involving prescription opioids and therefore it was deemed relevant for inclusion.

Due to the nature of the death investigation and data collection processes, more recent data on drug poisoning deaths was not available. The NDRDI extracts data from closed coronial files, resulting in a lack of timely data available on drug poisoning deaths. The establishment of a national electronic coronial database would assist in providing more timely data on drug poisoning deaths. Three quantitative studies included in this thesis are based on secondary analysis of existing data from the NDRDI, with the main source of this data being coronial data. Coronial data is collected for investigation of the death and not for research purposes, and so information that is of interest for research may not always be available. This may have introduced potential bias as a number of entries recorded as ‘unknown’ could potentially have been ‘yes’ or ‘no’ but the evidence was not available in the data sources. Limitations also include a reliance on individual coroners to implicate drugs in poisoning deaths, which can be challenging when multiple drugs are present on a toxicology report. However, the likely impact any potential bias may have had is expected to be minimal given that the coroners rely heavily on supporting information received from both the pathologist and the chemists in the State Laboratory. Information on whether the drugs were prescribed to the deceased or not is frequently not available in coronial files, which limits the assessment of illicit use of these drugs and the impact of illicit/street drugs on these deaths.

Methodologically, the greatest risk of bias to the observational studies conducted as part of this thesis is selection bias, which limits the generalisability of the results. The population in each of the observational studies (chapters 4 and 5) relate to the deceased; therefore, the study findings may not be representative of all people who use the drugs under investigation in this thesis. For example, the factors which were associated with pregabalin positive poisoning deaths, relative to non-pregabalin positive poisoning deaths, may not represent risk factors for drug

poisoning among people who take pregabalin. To minimise the risk of selection bias, the population should include all people who used drugs, or a random selection of same. This would allow for an assessment of risk factors associated with drug poisoning deaths involving the various drugs of interest. However, it is important to note that residual confounding would likely remain an issue, therefore any such analysis would have to be considered as hypothesis generating.

While including a random selection of people who use the drugs of interest would have addressed the risk of selection bias in this thesis, it was not considered feasible during the lifetime of a PhD due to the lack of a unique health identifier in Ireland. For example, if there was a unique identifier in Ireland it would have been possible to link data for people who were prescribed the drugs of interest in the PCRS to the NDRDI. Probabilistic matching, using name, date of birth, gender, and address, is an alternative to data-linkage using a unique identifier, and is possible in Ireland. However, previous experience using this methodology in Ireland, suggest that this can take several years to obtain the data and approvals (Cousins et al., 2016; Durand et al., 2020). A further challenge to data linkage in Ireland is the introduction of recent health research regulations; introduced in Ireland at the time when the General Data Protection Regulations (GDPR) came into effect. These health research regulations stipulate that such data linkage is not permissible unless a waiver is approved from the Health Research Consent Declaration Committee in the National Research Ethics Office of Research. Future studies, which do not have the strict time constraints of a PhD thesis should be undertaken to determine whether the factors identified in this thesis, remain when the issue of selection bias is addressed. It is however, important to note that any such studies will not entirely remove the risk of selection bias as the PCRS is means tested and overrepresents. The PCRS register includes data on medicines dispensed to citizens with full eligibility for the GMS scheme. 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. However, the PCRS-GMS pharmacy claims database funds the majority of pharmaceutical expenditure and represents the single largest pharmacy claims dataset in Ireland (Sinnott et al., 2017). As of 2015, almost 40% of the Irish population were covered by the GMS scheme (Sinnott et al., 2017).

In Chapter 3, lack of data on dispensing of private prescription drugs limited analysis to those dispensed through the PCRS-GMS scheme. The association

between dispensing rates of prescribed drugs and drug poisoning deaths involving these drugs was limited to benzodiazepines and antidepressants; however, these are the most commonly implicated drugs in drug poisoning deaths. In addition to the previously mentioned need for a unique health identifier, establishment of a national prescription drug monitoring system which includes both private and public prescriptions, would improve our knowledge in this area.

Lack of data on consumption of specific drugs (including prescription opioids, alcohol, cocaine, and heroin), stratified by sex, meant that evidence on associations of drug poisoning deaths with these drugs was limited.

Clients registered on the Irish national opioid agonist treatment register can remain registered for 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, in Chapter 3 it was not appropriate to assess the relationship between dispensing of prescription opioids using the national agonist treatment register data, and deaths involving prescription opioids.

In Chapter 5 the sample size for SDPD was limited to 129 men and 111 women, which may have limited the power of some associations. However, this could also be recognised as a strength of the study as all SDPD are reported to coroners; therefore, it is a complete census of SDPD in Ireland during the study period.

In Chapter 5, suicide data on drug poisoning deaths was included, therefore, findings pertaining to specific factors associated with SDPD may not be relevant to suicide deaths in general.

The association between drugs implicated in the deaths and both PPPD (Chapter 4) and SDPD (Chapter 5) are unadjusted, therefore, they may under or over-estimate the independent effects of drugs implicated as they lack appropriate adjustment. The power of some associations may have been low, and the possibility of residual confounding remains; therefore, only associations not causal effects can be inferred, and some evidence is; therefore, inconclusive. However, results from these studies may inform hypotheses for future research (see section 6.4).

Data used in the quantitative studies included in this thesis is retrospective, therefore it does not include analysis pertaining to how the COVID-19 pandemic may have affected drug poisoning deaths among women and men, especially among people who use drugs. In the USA, while data is not stratified by sex, there is

evidence of an increase in overall drug poisoning deaths present prior to the declaration of the COVID-19 pandemic, but a further increase in drug poisoning deaths appears to have accelerated during the pandemic, with synthetic opioids the main drug group driving this increase (Centers for Disease Control and Prevention, 2021). According to the Office for National Statistics (2021) data on drug-related deaths in Scotland showed an increase in the number of deaths among men from 2019 to 2020 but a slight decrease in the number of deaths among women.

Logistic regression analysis was used to evaluate the association between the binary outcome (e.g., SDPD or NSDPD) based on other independent variables in the dataset. This statistical relationship does not imply causation. Results displayed included a 95% confidence interval which provides a range of values within which we can be 95% certain contains the true population value. One could infer that results from the logistic regression analysis included in the studies in this thesis are hypotheses generating and that further research in the area of drug poisoning deaths is required.

6.3 Overall health research impacts

Using the Research Impact Framework, the impact of this thesis is outlined according to the four core domains of health research impacts: research-related, policy, health, and societal impacts (Kuruvilla et al., 2006).

6.3.1 Research-related impact

This thesis has contributed to knowledge on drug poisoning deaths among women and on the differences between men and women in relation to contributing factors and drugs involved in these deaths.

This thesis includes novel findings with inclusion of the first studies on drug poisoning deaths in Ireland with results stratified by sex, thus providing new evidence for an under-researched area of public health.

Three studies included in this thesis involved secondary data analysis. Consideration was given to undertake qualitative research in the area of women who use drugs; however, during the course of this PhD work, there were already two qualitative studies being undertaken in this area in Dublin (Ivers et al., 2021; Morton et al., 2020). Findings from these qualitative studies highlighted a reluctance among

women to engage with drug treatment services due to stigma, fear, and shame. In addition, one of the main factors affecting engagement with services was fear of losing their children through the involvement of social services, with lack of childcare facilities and previous negative experiences with service providers also expressed (Ivers et al., 2021; Morton et al., 2020). Results from these studies, including personal video clips from women who use drugs were included in various presentations I have given to stakeholders, as they complemented findings from this thesis by providing the user's perspective in relation to women who use drugs and reported barriers to accessing treatment.

Studies included in this thesis have resulted in four publications in high ranking (Q1) peer reviewed journals, as outlined at the beginning of the thesis. To date, work from this thesis has resulted in my involvement in a further scoping review on suicide deaths among people who use drugs, the protocol for which has been published (Murphy et al., 2021) and another study examining factors associated with suicide deaths among people who use drugs is currently underway.

The results from this thesis were also presented as poster and oral presentations at national and international academic conferences, listed at the beginning of this thesis. Moreover, research findings from this thesis were disseminated to key stakeholders using additional platforms such as publications in Drugnet Ireland (Appendices 3.1, 4.2 & 4.3). Drugnet Ireland is a quarterly drug and alcohol research and policy newsletter published by the Health Research Board. It provides summaries and analysis of recent publications and policy developments in addition to overviews of particular issues relating to the drugs and alcohol. While it is hard to measure any direct impact of these articles, Drugnet Ireland is distributed to various stakeholders throughout Ireland, including advocates and service providers for people who use drugs, as well as academics and policy makers.

In addition, presentations to key stakeholders allowed for more in-depth discussion and specific focus on issues raised from findings of the studies included in this thesis. This included presenting to students undertaking a diploma in Drug and Alcohol Studies, at the University of Limerick on three occasions during the course of this PhD. As most students undertaking this course work directly with people who use drugs, these sessions allowed dissemination of key findings and served to highlight pharmacokinetic and pharmacodynamic differences between men and women in relation to drugs interactions with the body in addition to highlighting

the importance of research and the impact research findings can have on policy and practice.

Acknowledgement of the importance of research included in this thesis was received with being awarded joint winner for oral presentation in the Clinical and Applied Research Section of the RCSI Research Day 2021 for the presentation on trends in drug poisoning deaths in Ireland, by sex (Chapter 3).

Following a request for supplementary materials, use of the scoping review and supplementary materials for an evidence-based medicine critical appraisal session with pharmacy students in the National University of Singapore highlights the translatability of this review into the education sphere.

In the area of research networking, following a presentation of findings from the cross-sectional study on factors associated with pregabalin positive poisoning deaths, by sex, at the Lisbon Addiction conference in 2019, an invitation was received and accepted to become a member of a European group on gender and drugs, coordinated by the EMCDDA in close collaboration with the Pompidou Group of the Council of Europe, the United Nations Interregional Crime and Justice Research Institute (UNICRI) and experts from various REITOX National Focal Points and countries. This group meets regularly with a focus to improve awareness on the importance of the inclusion of a gender perspective in the drug field and to increase scientific evidence in this area. Findings from this thesis, highlighting sex differences in drug poisoning deaths, was presented to this group. A side event attached to the Lisbon Addiction Conference 2022, focusing on the topic of gender and drugs, is being co-ordinated by this group.

Highlights from the study on trends in drug poisoning deaths is included in the HRB's 'Health Research in Action' annual publication 2021, which showcases work funded by the HRB and is written for a lay audience. This publication is published on the HRB website (www.hrb.ie) and was promoted widely on social media, in addition to being available in hard copy.

6.3.2 Policy impact

Having the opportunity to present key findings from this thesis to policy makers, such as the National Oversight Committee for the implementation of the national drugs strategy, the Department of Health's Drugs Policy and Social Inclusion Unit, the HSE Medicines Management Programme (MMP), and the Irish

Medical Council (IMC) ensures key policy makers are aware of the findings from this thesis and any changes in policy can be mapped by ongoing analysis of NDRDI data into the future.

Following the presentation of trend analysis (Chapter 3) to the National Oversight Committee for the implementation of the national drugs strategy, which is chaired by the Minister with responsibility for the national drugs strategy, it was agreed that future data analysis will include standardised rates per 100,000 population, in addition to absolute numbers of annual drug-related deaths. Furthermore, data will be stratified not only by sex but also by Community Healthcare Organisation areas, the regional health service delivery structures in Ireland to assist in planning services at regional level. The Minister, acknowledging the existence of barriers for women accessing drug and alcohol treatment services, recently announced extra funding for the provision of community-based drug and alcohol services for women (Department of Health, 2021). A recently published midterm review of the current national drugs strategy includes acknowledgement that the issue of gender and the specific needs of women has been raised by stakeholders (Drugs Policy and Social Inclusion Unit, 2021). This midterm review states that more gender specific and tailored initiatives and treatment pathways are required. Included in the programme for Government is a commitment to develop targeted interventions for women and to expand services for pregnant and post-natal women (Drugs Policy and Social Inclusion Unit, 2021).

Prior to the midterm review of the current national drugs strategy, I presented to the HRB Directorate of Health Information and Evidence, (of which, two staff members are on the National Oversight Committee for the national drugs strategy). This presentation provided a platform to highlight shortcomings in the current strategy to help prevent drug poisoning deaths. This included lack of women specific treatment services, and lack of visible timeframes and accountability for actions to be delivered in comparison to other national strategies related to other public issues, such as road safety. A further action from this presentation included use of presentation slides by a colleague in the HRB to complement a presentation to the Department of Health highlighting the need for electronic prescriptions in Ireland.

In my role as a member of the NOSP technical advisory group, I highlighted the importance of stratifying the data by sex. As a result, the first report to be

published on suicide deaths in Ireland to include those based on the balance of probabilities definition of suicide, will include data disaggregated by sex.

Presenting findings to the Health Products Regulatory Agency (HPRA) resulted in a new policy to improve collaboration between the HRB and the HPRA in relation to sharing data on deaths involving prescribable drugs. This will help contribute to evidence for the HPRA and should help provide an evidence base to improve appropriate use of licenced drugs. However, in relation to the findings of this thesis resulting in stricter regulations on specific drugs such as pregabalin, it was stressed to the HPRA that stricter regulations could also have a negative impact if alternative treatments were not offered. This was highlighted with the evidence from the trends in drug poisoning deaths involving benzodiazepines. There is evidence of a decrease in dispensing of benzodiazepines following stricter guidelines on prescribing of benzodiazepines; however, there was a corresponding increase in drug poisoning deaths involving benzodiazepines (Lynn et al., 2019). This potentially indicates that placing tighter restrictions on drugs that people can become dependent on, may drive users to illicit use of similar ‘street’ drugs. As ‘street’ drugs are generally more potent than licit drugs, they may contribute to an increased risk of drug poisoning. This unintended consequence of restricted prescribing of benzodiazepines has been reported as a key factor in the significant role of ‘street’ benzodiazepines in the rise in drug-related deaths reported in Scotland (McAuley et al., 2022).

At the presentation to the Irish Medical Council, the impact of multiple CNS depressant drugs in drug poisoning deaths, especially among women, was highlighted. Support to link NDRDI data to the HSE PCRS data was requested at this meeting. This would provide more information on the impact of both ‘street’ and prescribed drugs on drug poisoning deaths.

The NDRDI Steering Committee were presented findings from three studies using NDRDI data. Findings presented to the Committee contributed to correspondence, including recommendations from the Committee to the Minister with responsibility for the national drugs strategy, as well as the Minister with responsibility for mental health. Key stakeholders in the area of drug use, including representatives for families affected by drug use, are members of the NDRDI Steering Committee; therefore, it provided a platform to engage with families directly affected by drug use.

Having the opportunity to present findings from this thesis to the Coroner's Society of Ireland may help influence improvements in completeness of data collected as part of the death investigation, but also may influence their practice as General Practitioners (GPs), given that approximately 40% of coroners/deputy coroners are qualified GPs in Ireland. Lack of evidence on whether prescribable drugs implicated in drug poisoning deaths were prescribed to individuals was highlighted. In addition, a request was made to the coroners to collect data on the source of drugs involved in drug poisoning deaths as part of their death investigation to improve knowledge in this area so that evidence-based, appropriate public health interventions can be implemented.

6.3.3 Health service delivery impact

The protective factor of treatment for SUD against all types of mortality is well recognised; however, although women represent 3 in 10 people who use drugs worldwide, only 1 in 6 people in treatment for SUD are women (UNODC, 2021), with retention and completion of treatment significantly lower for women compared to men (Greenfield et al., 2017). Women have identified potential barriers to accessing treatment, which include the care of children and issues such as stigma, shame and guilt which can have negative effects on one's mental health (Ivers et al., 2021; Morton et al., 2020). In order to meet the needs of women, recommendations have been called for gender-specific approaches to treatment provision for SUD (EMCDDA, 2017). It has been highlighted that many treatment interventions do not take into account the special needs and considerations of women in treatment, particularly in terms of trauma and safety; therefore, some treatment interventions may not be as effective for women as they are for men (UNODC, 2021). However, women-only treatment provision may not be more effective than mixed-gender treatment (Greenfield et al., 2017). A more problem focused treatment approach related to issues predominantly among women, especially co-occurring psychiatric disorders, and specific needs for older women, may be more effective (Greenfield et al., 2017).

Further analysis of the data on drug poisoning deaths involving methadone shows that the proportion of deaths involving methadone among people registered on the OAT register increased from 35% in 2004 to 52% in 2017. While this may be an indication of a decrease in diversion of prescribed methadone into the illicit

market, it may also be an indication of inadequate methadone treatment dose leading people to take street methadone, in combination with prescribed methadone, to meet the needs of the individual prior to death. In fact, a recent global review of clinical practices in relation to OAT, suggests that many people attending OAT are prescribed doses below that considered optimal for clinical benefit (Jin et al., 2020). This is consistent with findings from two Irish cohort studies of patients receiving OAT in specialist addiction services and primary care where the median dose was lower than the recommended maintenance dose of 60-120 mg daily for 41% of patients (Durand et al., 2020), and 38% of patients (Cousins et al., 2016), respectively.

In addition, findings from the trends paper suggest a higher proportion of women whose death involved methadone, compared to men whose death involved methadone, were in receipt of prescribed methadone at the time of death. Therefore, consideration should be given to whether it may be more appropriate to provide gender-specific methadone dosing guidelines, accounting for the pharmacokinetic and pharmacodynamic differences between the sexes in relation to drugs, especially when more than one CNS depressant drug is being prescribed.

While methadone is a full opioid agonist, buprenorphine is a partial opioid agonist meaning that it only partially activates opioid receptors. Therefore, effects plateau at a specific dose, that is, after a certain point, taking more buprenorphine will not increase the effects of the drug. Due to this ceiling effect, it can cause less respiratory depression, and thus has lower overdose potential (Whelan & Remski, 2012). This means that, while it is a more expensive drug, it may be preferable than methadone for agonist substitution treatment for both men and women. Given that women experience a more enhanced effect from opioids than men, consideration should be given to increasing the availability of treatment using buprenorphine especially among women. Furthermore, to meet the needs of women accessing and completing treatment, current treatment systems could adopt more sex and age sensitive responses. These could include designated days and/or areas in treatment services for women with provision of appropriate childcare. In addition, increased awareness of a trauma-informed approach to the delivery of care. Being trauma-informed involves an understanding and acknowledgement of a service user's experiences of trauma in all aspects of service delivery, thus helping to avoid re-traumatizing the individual (Schmidt et al., 2018). It includes more focus on what has

happened to the person that may have contributed to their drug use instead of focusing specifically on their drug use.

The findings highlighted in Chapter 3 and Chapter 4 shows the impact of CNS depressant drugs, including alcohol, on drug poisoning deaths, especially among women. Encouraging healthcare professionals to consider both the pharmacokinetic and pharmacodynamic differences between the sexes in relation to drugs and their effects, and the patients' alcohol consumption, at the point-of-prescribing and supply of medications, could potentially reduce the risk of harm. Having had the opportunity to present findings from this thesis to GPs undertaking addiction service training, I hope the findings help improve health service delivery to individuals at high risk of drug poisoning deaths. In addition, I have also had the opportunity to present and take part in the panel discussion at a webinar on 'Benzodiazepines and Pregabalin Prescribing – How can we improve?' organised by the Irish College of General Practitioners, which facilitated dissemination of findings on this topic from studies included in this thesis, to an audience of almost 1200 online GP participants, including the President of the Coroners Society. I received positive feedback, including acknowledgement that change in prescribing practices among GPs is required and it highlighted the value of the research. Feedback from GPs working in the addiction services highlighted the lack of resources in the primary care setting to provide trauma-informed psychological approaches to enhance treatment.

I presented the findings from Chapter 4 (prior to publication) to the HSE MMP, which contributed to evidence-based information. The findings influenced a one-page information leaflet on appropriate prescribing of pregabalin which was disseminated by the HSE MMP to prescribers (HSE Medicines Management Programme, 2019). Of note, the September 2021 HPRA Drug Safety Newsletter included an article highlighting the association with concomitant use of pregabalin with opioids and/or other CNS depressants and reports of respiratory failure, coma, and deaths (Health Products Regulatory Authority, 2021).

Highlighting to coroners, some of whom are also GPs, the impact of prescribable drugs on drug poisoning deaths may also have influenced their work as GPs. Presenting findings from this thesis to the Irish Medical Council, which includes representation from the Department of Health, provided the opportunity to push the agenda to implement nationwide electronic prescriptions. This was discussed in some detail, highlighting the potential availability of illicit prescriptions due to the lack

of electronic prescription facilities, and the lack of a national prescription drug monitoring system. To facilitate restrictions incurred from the COVID-19 pandemic, the fast-track implementation of legislation to legalise the use of electronic prescriptions nationally did occur the month following the presentation. However, unfortunately, in Ireland there is still no unique health identifier and no national prescription drug monitoring system.

Findings from this thesis have influenced the perception of how data from national databases, including those in the area of drugs, which are maintained by the HRB, should be reported, resulting in more emphasis on the importance of including stratification by sex in reporting data.

I will continue to disseminate findings from this thesis to relevant stakeholders, including a plan to present findings to community pharmacists through the Pharmaceutical Society of Ireland in 2022.

6.3.4 Societal impact

The National Family Support Network (NFSN) collaborated as expert contributors to the scoping review, highlighting the negative effects on all family members following drug poisoning deaths. The NFSN also spoke about the need for more detailed research into drug-related deaths among women, which would enrich knowledge in this area, and contribute to this knowledge gap highlighted by families directly affected by drug-related deaths. Findings from the studies included in this thesis have been presented to representatives from the NFSN.

Merchants Quay Ireland is a voluntary organisation that helps people who are homeless and/or who have addiction issues. During the period 2020-2021 both Merchants Quay Ireland (in collaboration with University College Dublin) and Trinity College Dublin undertook qualitative studies exploring issues, challenges and experiences of women accessing treatment services for drug and alcohol treatment in Ireland (Ivers et al., 2021; Morton et al., 2020). Findings from these qualitative research projects, as outline in section 6.3.1 above, were included in presentations to various stakeholders. With agreement from Merchants Quay Ireland, to bring the human perspective into the findings from this thesis, video clips of women's stories, which included their perceived barriers to treatment, were included at the end of presentations where appropriate.

As also outlined in section 6.3.1, a summary of the published articles and additional supporting analysis were published in Drugnet Ireland. By reaching a wider audience through Drugnet Ireland, findings from this thesis may have the desired effect of increasing the knowledge base for people who use drugs with a view to influencing them to have a more open, engaging, and effective therapeutic relationship with their service provider.

Finally, as highlighted by Johnson et al. (2009), including disaggregation by sex (biological differences) and gender (social and cultural influences) in research studies not only guarantees more comprehensive research but it can also result in cost savings to the health care system by providing more effective evidence-based policies and practices, specifically related to sex and gender, and is a matter of social justice (Greaves et al., 1999; Johnson et al., 2009). An example of this is the need for sex and gender-specific drug treatment services. This could mean availability of women only services to ensure barriers to treatment are removed and effective, evidence-based services are appropriately provided to decrease drug-related deaths among women (Ivers et al., 2021).

6.4 Possible future research

Future research in the area of drug poisoning deaths, and in public health research in general should include, as a prerequisite, a specific requirement for research results to be stratified by sex. The dearth of knowledge on specific factors related to drug poisoning deaths among women was reported in Chapter 2. As highlighted in findings from this thesis, sex is an important factor that intersects with other social determinants in influencing susceptibility to drug poisoning deaths. However, sex-disaggregated data is still lacking not only in drug poisoning research but in the area of public health research in general. This was highlighted in relation to the data and research on the current COVID-19 pandemic with reporting of the data disaggregated by sex, rare (Heidari et al., 2020). Heidari et al. (2020) suggest that researchers have a moral and scientific responsibility to integrate sex and gender dimensions into their research, and others, including journal editors and research funding agencies, should commit to having a specific requirement for research findings to be stratified by sex.

Future research should consider examining if specific factors related to the COVID-19 pandemic such as negative psychological reactions, especially among the vulnerable groups (Cullen et al., 2020) which include women (Al Dhaheri et al., 2021) and restricted access to onsite treatment services, have impacted on drug poisoning deaths.

Ongoing monitoring of trends in drug poisoning deaths with data stratified by sex will enable the effects of any change in policy or practice to be assessed. Chapter 4 highlighted factors associated with pregabalin positive poisoning deaths, a drug which has increased significantly in drug poisoning deaths in recent years. Findings from this research have been disseminated to key stakeholders, including the IMC, the HPRA and the HSE MMP. These findings have also contributed to information leaflets disseminated to prescribers on appropriate use of pregabalin (Health Products Regulatory Authority, 2021; HSE Medicines Management Programme, 2019). The impact of any policy changes and/or changes to prescription guidelines, on drug poisoning deaths should be monitored in the future using an interrupted time series analysis (Beard et al., 2019).

'Street' drugs are of higher potency and have a shorter half-life than licenced drugs. Most 'street' drugs are CNS depressants, therefore, given the pharmacodynamic and pharmacogenetic differences between the sexes, future research on the general use of 'street' drugs through projects such as prevalence surveys, treatment demand data, drug use among prisoners and on the involvement of 'street' drugs in deaths, by sex is required. This sex-disaggregated data on 'street' drugs is necessary to have a comprehensive understanding of the current situation and to enable responses to be meaningful to both sexes. Linkage of drug-related deaths data from the NDRDI with prescription data from the existing prescription data (PCRS) in addition to data on private prescriptions, would improve our knowledge of the source of prescribable drugs implicated in drug poisoning deaths. This data could then be used in future research to provide more accurate data on the impact of 'street' prescribable drugs on drug-related deaths which include drug poisonings.

This thesis identified drugs associated with drug poisoning deaths. However, results from the logistic regression analysis included in the studies in this thesis are hypotheses generating and thus further research in the area of drug poisoning deaths is required. In addition, information on the source of these drugs and what

characteristics/factors contribute to differences between the group of people who died of drug poisoning deaths involving these drugs to those who live and use these drugs, is required. A cohort study involving people who use drugs, such as that in other EU countries including Norway and Austria, to further examine possible contributing factors to drug poisoning deaths, highlighted in this thesis, would be very appropriate. In addition, linking existing data across national databases, including SUD treatment data and drug dispensing datasets, could be used to further explore findings included in this thesis. This research could be carried out in countries where data linkage is possible, for example in Scotland or Norway (Merrall et al., 2012; Odsbu et al., 2020). Such research could be done in Ireland, but in the absence of a unique health identifier, this would require probabilistic data linkage using existing information in different datasets, such as demographics. This has been carried out in previous studies in the area of drug use in Ireland (Cousins et al., 2016; Durand et al., 2020). However, to be compliant to the health research regulations in Ireland, which were added onto GDPR, this would require a waiver from the Health Research Consent Declaration Committee in the National Research Ethics Office of Research. While this could take a number of years to complete, it would be appropriate to do this research.

As outlined in Chapter 4, despite women representing the minority of those in receipt of OAT, a high proportion of women relative to men who died of a drug poisoning death involving methadone were potentially in receipt of prescribed methadone. Findings reported in Chapter 4 show 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. Future research could provide a comprehensive report on what treatment is being provided to women and if there is an overreliance on pharmacotherapy for the treatment of co-occurring psychiatric conditions, especially the use of multiple CNS depressant drugs. As outlined in Chapter 1, women perceive sex-specific barriers to accessing treatment for substance use disorder. Addressing these barriers, in addition to advocating for a stronger therapeutic relationship between service provider and service user, could encourage women to access and receive appropriate treatment and support recovery. Future research evaluating sex-specific treatment provision could provide an evidence base on which future funding in the area of treatment provision enables treatment to be more accessible and more effective.

The aforementioned proposed research assessing the type of treatment provided, should preferably involve a quantitative research project, reviewing medical records. In addition to this quantitative research, a qualitative project should be undertaken. Given the barriers to accessing treatment identified by women, it would be of interest to assess the profile of women who are attending treatment services despite these barriers and compare their profile to that of their male peers in treatment. This would likely involve qualitative research in the format of interviews and focus groups. Given the supports required, the most appropriate people to work on this research project would be people in recovery from drug use. Not only could this empower people in recovery but also it may encourage a more open and honest engagement from participants.

A systematic review examining trauma-informed treatment for mental ill health reported eye movement desensitization and reprocessing, and cognitive behavioural therapy as the two most frequently used interventions (Han et al., 2020). Han et al. (2020) highlighted the inconsistent evidence supporting trauma informed interventions as an effective approach for psychological outcomes such as depression and anxiety, and more rigorous evaluation of trauma informed interventions for a range of trauma types and populations is required. The International Narcotics Control Board has highlighted the importance of gender-sensitive, trauma-informed, women-only substance abuse treatment programmes (INCB, 2016). Delivery of a trauma-informed service in a UK women-only residential treatment service for SUD, reported that while it is a valuable service, it can be challenging and requires significant resource investment (Tompkins & Neale, 2018). However, there is a dearth of research related to the effectiveness of treatment interventions, including trauma-informed interventions, designed specifically for women who use drugs.

Because women remain under-represented in treatment services, new studies on treatment effectiveness are needed to assess sex differences in response to different treatment strategies, including mixed versus single-sex treatment provision (Tuchmann, 2010).

Findings from Chapter 5 reported that being in receipt of treatment for substance use disorder had decreased odds of being associated with suicide drug poisoning deaths relative to non-suicide drug poisoning deaths among men only. As a result, this finding has informed a further study, currently underway (I am a

member of the research team undertaking this research), which is assessing factors associated with all means of suicide among people who use drugs in Ireland, with data stratified by sex. An overview of research looking at the biological, epidemiological and treatment outcome differences between men and women with substance use disorder reported higher rates of mental health issues, especially anxiety and/or depression among women relative to men who use drugs (McHugh et al., 2018). One of the provisional findings from this current study I am involved in, shows that women who use drugs are more likely to die by suicide relative to men who use drugs (Lyons et al., personal communication). This correlates with findings from a cohort study in the USA which reported an association between suicide and current substance use disorder for both men and women, with the strength of this association two to three-fold greater for women than men (Bohnert et al., 2017). Similar to data on drug poisoning deaths, suicide data is dominated by men, therefore future research on suicide should include sex stratified data to ensure specific risk factors for women are not masked by the data mainly on men.

6.5 Conclusion

This thesis highlights the current limited evidence on risk factors specific to drug poisoning deaths among women, and accurately describes the epidemiology of drug poisoning deaths among women in Ireland. The findings are important to a wide range of stakeholders including those who are affected by drug poisoning and associated premature deaths. The research provides much needed evidence to inform policy and practice interventions by identifying those at risk, identifying specific drugs influencing drug poisonings, and identifying risk factors associated with these unnatural and premature deaths, including suicide drug poisoning deaths, with data stratified by sex. Findings from this thesis should be used as evidence to support policy initiatives to reduce risk of drug poisoning deaths among both women and men. This includes early intervention, decreasing barriers to treatment, retaining people in treatment, appropriate use of CNS depressant drugs, in addition to enhanced psychological support, especially for people with dual diagnosis, and enhanced pain management. Drug poisoning deaths are unnatural, premature, potentially preventable deaths and findings from this thesis may also be used to

inform hypotheses for further research to enhance our knowledge in this area towards preventing further deaths.

Chapter 7: References from narrative part of thesis

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Chapter 8: Appendices

Appendix 1.1 Data sources for repeated cross-sectional studies

Data sources

Data was extracted from two large national databases, the National Drug-Related Deaths Index (NDRDI) and the Irish Health Service Executive (HSE) Primary Care Reimbursement Services (PCRS).

The National Drug-Related Deaths Index (NDRDI)

The NDRDI was established in September 2005 to comply with Action 67 of the 2001–2008 National Drugs Strategy. That action called for the development of a system for recording drug-related deaths and deaths among drug users to enable the State and its agencies to respond in a timely manner, with accurate data. The objectives of the NDRDI also include identifying and prioritising areas for intervention and prevention and measuring the effects of such interventions. The remit of the NDRDI was further expanded in January 2006 to include alcohol-related deaths and deaths of people who were alcohol dependent.

To ensure a complete and accurate Index, the NDRDI records data from four sources: the Coroner Service, the Hospital In-Patient Enquiry (HIPE) scheme, the Central Treatment List (CTL), and the General Mortality Register (GMR)/ Central Statistics Office (CSO) in order to ensure that the database is complete and accurate. The data is collected retrospectively on an annual basis.

NDRDI research staff undertake an annual census of all closed coronial files. In Ireland, a coroner has responsibility under the law to investigate the circumstances of all sudden, unexplained, violent, and unnatural deaths in order to establish the ‘who, when, where and how’ of the death. If a death is not immediately explicable, the coroner may order an autopsy to help establish the cause of death. Follow an autopsy, a coroner may proceed to an inquest to establish the identity of the deceased, how, when, where the death occurred and return a verdict. NDRDI research staff review all closed coronial files, onsite in coroners’ districts throughout Ireland. Depending on the type of death investigation, the file can contain extensive information, including autopsy and toxicology reports, depositions from family

members, friends, witnesses, and medical personnel. In addition to police reports and medical records where relevant. The inquest procedure can be a lengthy process and may not be concluded for a considerable period of time, therefore real time data is not achievable. Data relevant to the NDRDI are extracted from closed coronial files and entered onto an electronic database.

The Healthcare Pricing Office (HPO) of the Health Service Executive (HSE) manages the HIPE system in Ireland. The HIPE system is a health information system designed to collect clinical and administrative data on discharges from, and deaths in acute public hospitals across Ireland. Information is only recorded for people who are admitted as inpatients, therefore people who attend Accident and Emergency Units for treatment but die in Accident and Emergency Units prior to being admitted as inpatients, are not included in HIPE. Data from HIPE is used by policymakers, clinical teams, and researchers. Clinical data is coded using the 8th Edition of the International Statistical Classification of Diseases and Related Health Problems (World Health Assembly, 1966). An automated programme was developed by the HIPE department of the HPO in collaboration with NDRDI staff. This system facilitated an electronic download of data, on deaths which meet the NDRDI inclusion criteria. Data received from the HIPE scheme includes demographics and up to thirty diagnoses.

The Central Treatment List (CTL) is a national administrative database, established in 1998 under Statutory Instrument No 225 of the Misuse of Drugs (Supervision of Prescription and Supply of Methadone) Regulations (Government of Ireland, 1998), regulates the dispensing of methadone for opioid substitution treatment. These regulations were replaced in 2017 by Statutory Instrument No 522, to allow for the inclusion of buprenorphine medicinal products authorised for opioid substitution treatment (Government of Ireland, 2017). The CTL records demographic and clinical data on people in receipt of opioid agonist treatment, including methadone or buprenorphine in Ireland. An electronic download of data on deaths among people registered on the CTL is received by the NDRDI on an annual basis. Data received includes demographics, data pertaining to treatment including type of treatment provided, and date of death.

Every birth, death, and marriage occurring in Ireland must be registered with the General Register Office (GRO). The data on these registration forms is then forwarded to the Vital Statistics section of the Central Statistics Office (CSO) for the

production of statistics. The CSO categorises the cause of each death using the WHO diagnostic coding manual on the international classification of diseases (known as ICD categories). The tenth revision of this manual is currently used by the CSO. The CSO provide an annual electronic download of demographics and cause of death of all registered deaths that meet the inclusion criteria for the NDRDI. In addition, the cause of death for data received from other data sources for the NDRDI can be verified through the General Deaths Register in the CSO. Data received from the CSO includes demographics, occupation, employment status and cause of death.

Cases from the different data sources are crossmatched on a selection of variables, including name, gender, county of residence, date of birth and date of death. This allows the NDRDI to eliminate duplicates and to maximise the amount of information available on each case recorded on the database.

For deaths which occurred from 2015 onwards, the National Office for Suicide Prevention (NOSP) have requested the Health Research Board to expand the NDRDI data collection from coronial files to include all deaths with a verdict of suicide or a record of suicide based on the balance of probability that the deceased took their own life. This broader definition of suicide is based on the Rosenberg et al.,(1988) operational criteria for the determination of suicide. The process undertaken to include deaths based on the balance of probability was validated by a team, which included a national expert and an international expert in the area of suicide. In addition, a number of deaths included based on the balance of probability were reviewed by an expert review group to confirm that they met the inclusion criteria. Inclusion of the broader definition of suicide, allows, for the first time in Ireland, more robust analysis on suicide drug poisoning deaths. This analysis would contribute to a greater understanding of these deaths, with particular reference to quantifying the impact of known risk behaviours including the impact of drugs, by sex.

The Health Service Executive (HSE) Primary Care Reimbursement Services (PCRS)

The HSE PCRS register includes data on medicines dispensed to citizens with full eligibility for the General Medical Services (GMS) scheme. 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. However, the HSE PCRS-GMS pharmacy claims database funds most of pharmaceutical expenditure and represents the single largest pharmacy claims dataset in Ireland (Sinnott et al., 2017). 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. 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. As of 2015, almost 40% of the Irish population were covered by the GMS scheme (Sinnott et al., 2017).

The latest published data (Health Research Board, 2019) from the NDRDI shows that the percentage of women who died as a result of drug(s) poisoning has stabilized but more in-depth analysis looking at what drugs were involved in these deaths and if there were any evidence of change in drug habits would give more insight into how policy can help decrease these deaths.

Supplementary Table 1.1 Data sources characteristics

Data Source	Participants	Setting	Data contributors	Limitations	Strengths
National Drug-Related Deaths Index (NDRDI)	*People in the general public who died from* • Illicit drug poisoning deaths • Alcohol drug poisoning deaths • Prescribable drug poisoning deaths *People with a lifetime history of drug use and died from* • Traumatic causes • Medical causes	Deaths in the general population in the republic of Ireland Deaths among people who use drugs	• Closed coronial files • OAT register • Hospital inpatient data • General Mortality Register	• Lack of timely data • Reliance on coroners to implicate drugs • Lack of standard practices among coroners	• Complete data on deaths due to poisonings • Complete data on deaths among people registered on the OAT register
The Health Service Executive (HSE) Primary Care Reimbursement Services (PCRS)	Citizens with full eligibility for the General Medical Services (GMS) scheme. Eligibility for the GMS is mainly through means-testing and age (youngest and oldest population cohorts)	Medicines dispensed to citizens with full eligibility for the General Medical Services (GMS) scheme	• GPs • Community pharmacies • Dentist • Optometrists/ ophthalmologist	Over-represents the • More socially deprived • Younger aged population • Older aged population Does not include data on private prescriptions dispensed or hospital prescriptions	• Funds the majority of pharmaceutical expenditure nationally • Is the single largest pharmacy claims dataset in Ireland • 40% of general population covered by GMS scheme

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Appendix 2.1 Drug poisoning deaths among women: scoping review protocol

Introduction

Detailed segregated data on drug-related harms by men and by women, which include drug poisoning deaths, are lacking (International Narcotics Control Board, 2017); (EMCDDA, 2015); (United States, 2017). This gap in knowledge may mask important differences between men and women in drug poisoning deaths and associated risk factors (Masters et al., 2017).

One third of people who misuse drugs (both licit and illicit) globally are women (International Narcotics Control Board, 2017); (United Nations, 2018). In 2016 there were 63,632 drug poisoning deaths reported in the US with the age-adjusted rate for drug-poisoning deaths for males (26.2 per 100,000), almost double that of females (13.4) (National Center for Health Statistics, 2018). According to the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA), 8,238 drug poisoning deaths (22% women, 78% men) were reported in EU countries in 2016 (EMCDDA, 2019). The EMCDDA (2019) suggest that due to, underreporting in some EU countries, different methodologies in toxicology analysis and differences in registration processes that can lead to reporting delays, these estimates may represent an underestimate of the true prevalence; therefore, drug poisoning deaths remain a major challenge for public health policy. Although the absolute numbers are higher in men, epidemiological trends have shown that drug poisoning deaths among women have increased at a higher rate relative to men, especially in relation to intentional drug poisoning deaths (Tyrrell et al., 2017); (Osborn, 2018). To develop effective policy and practice responses to drug use and associated mortality among women, it is vital that evidence is stratified by sex (Clark et al., 2015); (Mazure and Fiellin, 2018) as the biological, social and psychological differences between men and women can have an impact on all aspects of drug misuse (Tuchman, 2010).

Study Rationale

The importance of sex-specific drug policies and treatment services, and of exploring the particular needs and challenges among women who use drugs, has been highlighted (United Nations, 2018); (Bawor et al., 2015). A report from the Office

on Women's Health in the United States suggests that the practice of relying on services, that were designed for men, to meet the needs of women who use drugs is not appropriate (United States, 2017). One factor of concern is evidence that women tend to progress from drug use to drug dependence quicker than men (Back et al., 2011); (Clark et al., 2015), therefore more knowledge on risk factors associated with drug use and drug-related mortality among women, in addition to access to sex-specific treatment at an early stage, is important.

Factors that contribute to drug poisoning deaths among women are likely to be multi-faceted, therefore, a review of the nature and extent of the research that has been examined in this area is warranted. There are currently no reviews on this topic. A scoping review approach was deemed suitable as there is limited clarity on the extend, range and nature of evidence on risk factors associated with drug poisoning deaths among women. Scoping reviews are an increasingly popular form of knowledge synthesis that aim to systematically search and map the breadth of available evidence, categorise key concepts, identify knowledge gaps and research deficits, and propose recommendations to guide future research (Colquhoun, 2012); (Peters et al., 2015). In this sense, a scoping review is an ideal approach toward a comprehensive understanding of drug poisoning deaths among women. In addition, limited data on risk factors for drug poisoning deaths among women has implications for policy and practice; understanding specific factors associated with drug poisoning deaths among women are critical precursors to developing targeted interventions and prevention strategies.

Objectives

The objective of this review is to map the extent, range, and nature of evidence in relation to drug poisoning deaths among women to inform future research, policy, and practice. In addition, this review will aim to identify gaps in knowledge for future research.

Methods

The methodological five-stage framework, (1) identifying the research question, (2) identifying and retrieving relevant studies, (3) study selection, (4) charting the data, (5) collating, summarizing, and reporting the results, and the sixth optional consultation stage, developed by Arksey and O'Malley (2005) and updated by Levac

et al (2010) and (Daudt et al., 2013), will be used to guide this scoping review. The scoping review will be reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Extension for Scoping Reviews (PRISMA-ScR) (Tricco et al., 2018).

Stage 1: Identify the research question

Scoping review research questions are expected to be sufficiently broad in nature to capture the breadth or research on a given topic (Arksey and O'Malley, 2005); (Levac et al., 2010) therefore this review will seek to establish what is known from existing literature about drug poisoning deaths among women, what research designs are used to study this phenomenon and finally, what gaps remain in knowledge and recommendations for further research and changes to policy and practise.

Definition of drug poisoning deaths

For the purpose of this scoping review, 'drug poisoning deaths' will include all manners of death (among women) directly due to the toxic effects of drugs, otherwise known as 'direct drug induced' or 'overdose' deaths.

Stage 2: Identify and retrieve relevant items

The search strategy will be developed in collaboration with an information specialist. It will involve both published, unpublished (where relevant) and grey literature. To encompass all necessary index terms (Mesh terms), keywords and phrases, an initial, limited search will be undertaken using MEDLINE and EMBASE search engines. Search strings will be adapted and bibliographic databases; MEDLINE, EMBASE, CINAHL and Web of Science will be searched for relevant publications. Alerts will be maintained on search engines. This search will be supplemented by searches of grey literature; relevant websites such as the EMCDDA (http://www.emcdda.europa.eu/); updates from specialised libraries (such as the Health Research Board (HRB) National Drugs Library (http://www.drugsandalcohol.ie/); conference/event attendance; and through consultation with experts in the area. Experts will include representatives from the National Drug-Related Deaths Index Steering Committee and experts in the area from the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA). A search

of the reference lists of all included items will be undertaken. All results will be imported into and managed using Endnote bibliographic management software.

The inclusion and exclusion criteria for the scoping review will be developed through an iterative process as the series of searches progressed. There are various definitions used internationally for drug-related deaths. For the purpose of this scoping review, ‘drug poisoning deaths’ include all manners of death (among women) directly due to the toxic effects of drugs, otherwise known as ‘direct drug induced’ or ‘overdose’ deaths.

Publications identified will be assessed as follows: The criteria for inclusion involved identifying literature that contained data on drug poisoning deaths among women. One of the objectives of this scoping review is to highlight recommendations for policy and practice to help decrease drug poisoning deaths among women, therefore the timeframe for the search will be limited to twenty years as more up-to-date research is considered more relevant. Peer-reviewed and non-peer reviewed publications will be included if they were published from 01 June 1998, were written in English, and involved humans.

Non-fatal drug poisonings, fatal poisonings related only to alcohol and/or tobacco, and mortality within randomised controlled clinical trials or due to medical errors will be excluded. Other non-drug poisoning deaths among people who use drugs will be excluded. This included for example, deaths due to trauma or medical causes such as liver disease or human immunodeficiency virus infection. Epidemiological publications which failed to stratify drug poisoning death results by sex will be excluded.

Stage 3: Study selection

The study selection process will be outlined as per PRISMA-ScR guidelines. All results from the search strategy will be imported into Endnote and duplicates will be removed. Reviewers EL and AD will discuss the inclusion/exclusion criteria and apply it to a sample of 100 items to assess consistency. All titles and abstracts will then be reviewed by one reviewer (EL) to determine potential eligibility. The second reviewer (AD) will then review all excluded title and abstracts to ensure no items were missed. Full text publications will then be reviewed independently by two reviewers (EL, AD). Any uncertainly in relation to publication eligibility will be resolved through discussion

firstly between the two reviewers and if required, with the other authors until a consensus is reached on the final selection.

Stage 4: Charting the data

Data charting will involve extracting relevant data from full text publications reviewed. A tailored data charting tool will be developed using excel and agreed by review team a priori. The following data will be collected using the charting tool;

- study characteristics, such as authors, title, year of publication, and country of origin
- aim/objectives of the study
- study design
- study population
- study setting
- sample size
- area of research
- type of drugs involved
- definition used for drug poisoning death
- key results/ candidate factors identified
- gaps in research identified
- policy and/or practise implications identified
- reason for exclusion
- reviewer comments

The publications will be examined and sorted according to key issues and candidate factors emerging. The first reviewer (EL) will chart key data from the fully reviewed publications using the data charting form. The format of the data charting tables, and the data identified for extraction will be informed by the purpose of the scoping review and, as with the other stages, this will be an iterative process, thus may be refined as the charting of this scoping review progresses. Publications will be excluded if the reviewers agreed that there was insufficient data on the topic. The final selection for inclusion will be agreed by both reviews.

Stage 5: Collating, summarising, and reporting

As recommended by Arksey and O'Malley (2005), the authors will not assess the quality of the evidence included, instead, the data will be collated and summarised in accordance with the overall aim and objectives of the study. A narrative account of the findings will be presented including basic descriptive analysis and thematic outcomes developed from key findings. Numerical analysis will include geographical distribution, drugs involved, the type of evidence available and study designs of the publications included. Data from the included publications will be coded according to the drug(s) involved in the reported deaths. Specific candidate factors or themes identified will be allocated specific codes which will be used to summarise common candidate factors/themes which appear to be associated with drug poisoning deaths among women. In addition, themes in relation to gaps in research and considerations for policy and practice to help decrease drug poisoning deaths among women, will be extracted.

Stage 6: Consultation exercise

In order to obtain additional input and to gain perspectives and insights beyond those obtained through data charting, consultation will take place with national experts from the Irish National Drug-Related Deaths Index (NDRDI) Steering Committee and international experts from the EMCDDA. This will help ensure inclusion rigour and will give the opportunity to inform important stakeholders that this study is being undertaken and results will be disseminated when complete.

Conclusion and Dissemination

To our knowledge this is the first scoping review on drug poisoning deaths among women and it will provide an important foundation on knowledge in this area. The objective of this review is to gain a comprehensive understanding of the extent, range, and nature of evidence in relation to drug poisoning deaths among women to inform future research, policy, and practice. In addition, it will aim to identify gaps in knowledge for future research. A limitation of using the scoping review methodology is that it does not include a quality assessment of the publications included, however it does have the capacity to capture a breadth of evidence in an area where there are limited peer-review publications.

This review will be submitted for publication in a peer reviewed academic journal, presented to stakeholders, and will be submitted for presentation at suitable conferences.

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Appendix 2.2 Supplementary Table A Characteristics of Primary Studies Included (*n* = 50)

Author and year	Country	Focus of study	Study type/data resource	Description of sample*	Candidate factor(s) identified as associated with poisoning deaths among women
Isacsson et al. 1999	Sweden	The use of psychotic drugs among men and women who commit suicide	Retrospective secondary data analysis of toxicology screening in 5281 suicides 1992-1994	5281 suicide deaths of which 1840 were poisoning deaths (756 women, 1084 men)	In this primary study by Isacsson et al. 1999, the following candidate factors was identified as playing a role in psychotic drugs poisoning deaths by suicide among women; women tended to: • be aged 45-59 years • have antidepressants involved in their death • have a higher percentage of deaths linked to suicide
Oyefeso et al. 2000	England and Wales	Fatal antidepressant overdose among drug abusers and non-drug abusers	Retrospective secondary data analysis of coronial data through a special death register Jan -June 1998	491 deaths (124 women, 367 men)	In this primary study by Oyefeso et al. 2000, the following candidate factors were identified as playing a potential role in antidepressant drug poisoning deaths; women tended to: • be overrepresented in antidepressant drug poisoning deaths • be more likely to receive an open or suicide verdict • have 2 or more drugs implicated in their death
Shah et al. 2001	England and Wales	Deaths from antidepressants in England and Wales 1993-1997	Retrospective secondary data analysis of coronial data and data on antidepressant prescription numbers	2503 in total (rates per million by sex provided: 9.6 per million women, 9.9 per million men)	In this primary study by Shah et al. 2001, the following candidate factor was identified as playing a potential role in poisoning deaths involving antidepressants; women tended to: • be aged 45-59 years
Shah et al. 2001	England and Wales	Trends in deaths from drug overdose and poisoning in England and Wales 1993-1998	Retrospective secondary data analysis of coronial data	15720 deaths (5497 women and 10223 men)	In this primary study by Shah et al. 2001, the following candidate factors were identified as playing a potential role in poisoning deaths; women tended to: • have the highest mortality rate for opioid poisoning in the age group 25-34 years • experience an increase in mortality rate with an increase in age for benzodiazepine poisoning deaths • have the highest mortality rate for paracetamol poisonings in the age group over 65 years • have the highest mortality rate for antidepressant poisonings in the age group 35-44 years • have a higher proportion of antidepressant drugs involved in poisoning deaths followed by paracetamol

					• have a higher rate of poisoning deaths in residence in area of deprovision
Quaglio et al. 2001	Italy	Cause of death among a large cohort of heroin injecting drug users (IDUs) presenting to intervention services	Retrospective secondary data analysis of mortality data 1985-1998	2708 deaths from all-cause mortality - Inc. 1001 OD deaths (125 women, 876 men)	In this primary study by Quaglio et al. 2001, the following candidate factor was identified as playing a role in drug poisoning deaths among people who inject drugs; women tended to: • be at a higher risk of a drug poisoning death if they have dropped out of treatment
Shah et al 2002	England and Wales	Trends in suicide from drug overdose in the elderly in England and Wales	Retrospective secondary data analysis of data from the Office for National Statistics (ONS) database 1993-1999	1864 suicide deaths from drug OD in over 65yr olds (1154 women, 710 men)	In this primary study by Shah et al. 2002, the following candidate factors were identified as playing a role in drug poisoning deaths in the elderly; women tended to: • represent the highest number of drug poisoning deaths in those aged 65 years and older • have paracetamol and associated compounds (particularly co-proxamol) involved in drug poisoning deaths • have the highest overall suicide rate in the age group 65-74 years within this elderly study group
Preti et al. 2002	Italy	Deaths by unintentional illicit drug overdose in Italy, 1984-2000	Retrospective secondary data analysis of surveillance data: official statistics data and medical examiners data	9981 total deaths: no breakdown of numbers of deaths by sex. Death rates by sex given.	In this primary study by Preti et al. 2002, the following candidate factors were identified as playing a role in unintentional illicit drug poisoning deaths; women tended to: • have the highest death rate in the age group 25-34 years • have the greatest increase in deaths over the reporting periods was in the age group 35-44 years
Davidson et al. 2003	United States	Fatal heroin-related overdose in San Francisco, 1997-2000	Retrospective secondary data analysis of medical examiner's case files for opioid-positive death	333 deaths (43 women, 290 men)	In this primary study by Davidson et al. 2003, the following candidate factor was identified as playing a role in heroin poisoning deaths; women tended to: • have the highest number of deaths in the age group 16-30 years
Bird et al. 2003	Scotland	Drug-related deaths in Scotland among people who inject drugs	Retrospective secondary data analysis using national statistics	332 Deaths (65 women, 267 men)	In this primary study by Bird et al 2003, the following candidate factor was identified as playing a potential role in poisoning deaths among people who inject drugs; women who inject tended to: • have a lower risk of drug poisoning death than men who inject drugs

Bryant et al. 2004	United States	Methadone and heroin overdose related deaths in New York, 1990-1998	Retrospective secondary data analysis of data from the Office of the Chief Medical Examiner on accidental drug overdose deaths	7451 deaths (1531 women, 5920 men)	In this primary study by Bryant et al. 2004, the following candidate factor was identified as playing a role in methadone or heroin accidental drug poisoning deaths; women tended to: • have a greater likelihood of methadone-induced poisoning death
Gunnell et al. 2004	England	Deliberate drug overdose and death in hospital 1997-1999	Retrospective secondary data analysis of routinely collected Hospital Episode Statistics data	1146 deaths (569 women, 577 men)	In this primary study by Gunnell et al. 2016, the following candidate factor was identified as playing a role in poisoning deaths; women tended to: • be older than their male counterparts with a mean age of 58.2 years for women and 56.5 years for men with the highest deaths rate for women in the age group >75 years
Shah et al. 2005	United States	Unintentional methadone-related overdose death in New Mexico (USA) 1998-2002	Retrospective secondary data analysis of data from the Office of the Medical Investigator and the Toxicology Bureau of the Scientific Laboratory Division	1120 deaths (253 women, 867 men)	In this primary study by Shah et al. 2005, the following candidate factor was identified as playing a potential role in methadone poisoning deaths; women tended to: • have methadone co-intoxication with prescription drugs involved in drug poisoning deaths
Morgan et al. 2006	England and Wales	Heroin and methadone use and fatal poisoning in England and Wales 1993-2004	Retrospective secondary data analysis of mortality data, drug seizure data and drug prescription data	7072 deaths involving heroin/morphine (14% [n=990] women, 86% men) and 3298 deaths involving methadone (17% [n=561] women, 83% men).	In this primary study by Morgan et al. 2006, the following candidate factor was identified as playing a role in poisoning deaths; women tended to: • be slightly older (mean of 1 year) than their male counterparts with the highest deaths rate for women in the age group 15-34 years
Shah et al. 2008	United States	Unintentional drug overdose death in New Mexico, USA, 1990-2005:	Retrospective secondary data analysis of data in the Office of the Medical Investigator	2954 unintentional deaths (679 women, 2275 men)	In this primary study by Shah et al. 2008, the following candidate factors were identified as playing a potential role in unintentional drug poisoning deaths; women tended to: • have prescription opioids involved in drug poisoning deaths

					• have a high representation of white females, Hispanic females, and American Indians • have an increase in deaths involving polydrugs reported, especially in white females
Wunsch et al. 2009	United States	Opioid and other prescription drug related accidentally drug poisoning deaths in rural Virginia	Retrospective secondary data analysis of medical examiner case records 1997-2003	889 deaths (37% women, 63% men)	In this primary study by Wunsch et al. 2009, the following candidate factors were identified as playing a potential role in prescribed opioid poisoning deaths; women tended to: • be older than men, with a mean age of 42.8 years compared to 38.5 years for men • have a higher proportion of suicide deaths • have a higher proportion of antidepressant drugs present on toxicology compared to men • be mainly urban dwellers • be in employment
Piercefield et al. 2010	United States	Unintentional deaths from medication overdose in Oklahoma, 1994-2006	Retrospective secondary data analysis of medical examiner records on fatal unintentional poisonings	2112 deaths (824 women, 1288 men)	In this primary study by Piercefield et al. 2014, the following candidate factors were identified as playing a role in unintentional prescription or over-the-counter drug poisoning deaths; women tended to: • be older than their male counterparts, with a median age of 44 years for women comparted to 40 years for men • have a higher increase in death rate over the reported period compared to men • represent an increasing proportion of prescription opioid poisoning deaths during the reporting period
Green et al. 2011	United States	Fatal opioid intoxications in Connecticut, USA: 1997-2007	Retrospective secondary data analysis of mortality data from the Office of the Chief Medical Examiner	2900 deaths (759 women, 2141 men)	In this primary study by Green et al. 2011, the following candidate factors were identified as playing a potential role in opioid poisoning deaths; women tended to: • have methadone involved in their death • have poly opioid poisoning deaths
Värnik et al. 2011	16 European Countries	Rates of suicide by drug self-poisoning in 16 European countries	Retrospective secondary data analysis of data collected from national statistics offices in each country 2000-2005	5091 deaths (2,580 women and 2,511 men)	In this primary study by Värnik et al. 2011, the following candidate factor was identified as playing a potential role in suicide drug poisoning deaths; the majority of women tended to: • be aged 45-54 years
Zamparutti et al. 2011	United Kingdom	Deaths of opiate/opioid	Retrospective secondary data analysis of coronial	584 deaths (125 women, 459 men)	In this primary study by Zamparutti et al. 2011, the following candidate factors were identified as playing a role in prescribed opioid poisoning deaths; women tended to:

		misusers involving dihydrocodeine	data in the Special Mortality Register 1997-2007		• have a higher proportion of suicide deaths • have used 2 or more drugs
Bird & Robertson 2011	Scotland	Toxicology of Scotland's drugs-related deaths in 2000-2007, specifically those where heroin, methadone, diazepam and/or alcohol were present	Retrospective secondary data analysis using national statistics	2893 (535 women, females = 535)	In this primary study by Bird & Robertson 2011, the following candidate factors were identified as playing a potential role in poisoning deaths; women tended to: • have opioids, mainly methadone, present on toxicology • have a higher percentage than men of deaths where neither heroin, methadone, diazepam, or alcohol was involved.
Sinyor et al. 2012	Canada	Substances used in completed suicide by overdose in Toronto	Retrospective secondary data analysis of coroners' files	397 suicides by overdose (197 women, 199 men)	In this primary study by Sinyor et al. 2012, the following candidate factors were identified as playing a role in suicide drug poisoning deaths; women tended to: • be slightly older than men, with a mean age of 49.8 years compared to 48.3 years for men • have a history of mental illness, most commonly depression • have a history of a previous overdose
Mack et al. 2013	United States	Overdoses of Prescription Opioid Pain Relievers and Other Drug related deaths Among Women	Retrospective secondary data analysis of the National Vital Statistics System files.	15,323 deaths among women attributed to drug overdose 1999-2010	In this primary study by Mack et al. 2013, the following candidate factors were identified as playing a role in drug poisoning deaths for women; women tended to: • be aged 45-54 years • have one or more prescription drugs involved in their death • have high rates of opioid pain relievers involved in their death • have a high rate of drug poisoning deaths linked to suicide • have high rates of drug poisoning deaths represented by non-Hispanic white, American Indian or Alaska identity
Binswanger et al. 2013	United States	Mortality after prison release: 1999 to 2009	A retrospective secondary data analysis of a cohort of ex-prisoners	558 overdose deaths (122 women, 436 men)	In this primary study by Binswanger et al. 2013, the following candidate factors were identified as playing a role in poisoning deaths; women tended to: • be at an increased risk of poisoning death if they have been incarcerated compared to men • be at an increased risk of opioid-related poisoning death post release from prison compared to men

Calcaterra & Binswanger 2013	United States	National trends in psychostimulant-related deaths: 1999-2009	Retrospective secondary data analysis of US national mortality data	15514 total deaths: no breakdown of numbers of deaths by sex. Death rates by sex given	In this primary study by Calcaterra & Binswanger, 2013, the following candidate factor was identified as playing a role in psychostimulant poisoning deaths; women tended to: • have the highest death rate in the age group 35-44 years
Algren et al. 2013	United States	Fentanyl-associated deaths	Retrospective secondary data analysis of medical examiner and toxicology database	101 FHF (of which 39, (39%) were women) and 90 NFHF(of which 17, (19%) were women) in analysis.	In this primary study by Algren et al. 2013, the following candidate factors were identified as playing a role in fentanyl-associated poisoning deaths; women tended to: • be more likely to have fentanyl-contaminated heroin implicated in their death compared to men • be aged over 44 years • be divorced or widowed • be urban dwellers • have a more pronounced clinical effect and higher risk of toxicity from opioids then men
Gjersing et al. 2013	Norway	Drug-related deaths in an urban setting in Oslo, Norway	Retrospective secondary data analysis of multiple registers	231 deaths (51 were women)	In this primary study by Gjersing et al. 2013, the following candidate factors were identified as playing a role in drug poisoning deaths for women living in an urban setting; women tended to: • be older than men, average age 40.2 years v's 36.5 years • have prescription opioids involved in their death • have been in contact with health/social service within a year of death • be city dwellers
Origer et al. 2013	Luxembourg	Opiate- and cocaine-related fatal overdoses in Luxembourg	Retrospective secondary data analysis of law enforcement data, drug use surveillance and forensic data 1985-2011	340 deaths (63 women, 238 men)	In this primary study by Origer et al. 2013, the following candidate factors was identified as playing a role in opiate and cocaine poisoning deaths; women tended to: • younger than men • depend on sex work to fund income • have more psychotropic drugs present on toxicology • have used 2 or more drugs • have a faster escalation from first use to problematic use to drug poisoning death than men

Lovrecic et al. 2013	Slovenia	Drug-related deaths in Slovenia: a comparison between treatment contacts and non-treatment contacts	Retrospective secondary data analysis of data from treatment records, the Special Mortality Register and the General Medical Register 2004-2006	223 deaths (but only 36 women) 134 Direct DRD (i.e., poisonings) of which only 5 were women	In this primary study by Lovrecic et al. 2013, the following candidate factor was identified as playing a potential role in poisoning deaths; women tended to: • be less well represented in deceased treated people with respect to deceased untreated people who used drugs
Rudd et al. 2014	United States	Deaths associated with heroin overdose	Retrospective secondary data analysis of State mortality data using the National Vital Statistics System	large sample, rates provided	In this primary study by Rudd et al. 2004, the following candidate factor was identified as playing a role in opioid drug poisoning deaths; the majority of women tended to: • have died from poisoning death involving prescription opioids
Borriello et al. 2014	Italy	Drug-related deaths in Campania (Italy) 2008-2012	Retrospective secondary data analysis of toxicological reports on drug related deaths observed at Second University of Naples	267 deaths (16 women, 251 men)	In this primary study by Borriello et al. 2014, the following candidate factors were identified as playing a role in drug poisoning deaths; women tended to: • have the highest incidence of death in those over 35 years • have multiple illicit drugs involved in their death • have alcohol commonly involved in their death
Gjersing, L. & Bretteville-Jensen, A. L. 2014	Norway	Mortality and risk factors in a 13-year cohort study of street-recruited injecting drug users 1997-2010	Prospective cohort study	45 deaths (8 women, 37 men) deaths, of which 25 (5 women, 20 men) were due to poisonings	In this primary study by Gjersing & Bretteville & Jenson 2014, the following candidate factors were identified as playing a potential role in poisoning deaths; women tended to: • have sex work identified as a risk factor for death • have injected heroin • have used heroin with other prescription drugs and/or alcohol • have a reduced risk of death if in receipt of treatment
Hassanian-Moghaddam et al. 2014	Iran	Adult and adolescent poisoning in Tehran, Iran; 2006 and 2011	Retrospective secondary data analysis of acute poisonings in a hospital setting.	2109 deaths (627 women, 1,482 men)	In this primary study by Hassanian-Maghoddam et al. 2014, the following candidate factor was identified as playing a role in drug poisoning deaths; women tended to: • have drugs which affect the gastrointestinal system implicated more frequently in drug poisoning deaths
Pierce et al. 2015	England	Mortality rate in a large cohort of people who used	Retrospective secondary data analysis of treatment data linked to mortality data.	1715 deaths (375 women, 1353 men)	In this primary study by Pierce et al. 2015, the following candidate factor was identified as playing a role in drug poisoning deaths among people who used opioids; women tended to:

		opioid in England 2005-2009			• have a lower risk of drug poisoning death compared to men, however this lower risk is less evident in women aged over 35 years
Roxburgh et al. 2015	Australia	Accidental and intentional codeine overdose deaths	Retrospective secondary data analysis of coronial data including toxicology reports, from the National Coronial Information System 2000-2009	1437 deaths (717 women, 720 men)	In this primary study by Roxburgh et al. 2015, the following candidate factor was identified as playing a potential role in codeine poisoning deaths; women tended to: • be overrepresented in intentional codeine poisoning deaths
Petrushevska et al. 2015	Republic of Macedonia	Overdose and drug related fatalities involving opioids and benzodiazepines in the Republic of Macedonia	Retrospective secondary data analysis of toxicology reports 2002-2013	165 deaths (20 women, 145 men)	In this primary study by Petrushevska et al. 2015, the following candidate factors was identified as playing a role in opioid and/or benzodiazepine drug poisoning deaths; women tended to: • have opioids as the main drug group involved in poisoning deaths • be older than men with a mean age of 31.75 years compared to 27.77 years for men • have more psychotropic drugs involved in poisoning deaths than men
Metz et al. 2016	United States	Maternal Deaths from Suicide and Overdose in Colorado, United States	Retrospective secondary case series data analysis of pregnancy associated deaths due to self-harm (accidental overdoses and suicides) using death certificates, coronial, prenatal care, and hospital records 2004-2012	211 Maternal deaths, only 44 had positive toxicology with 31 deaths classified as accidental overdose with an additional 5 classified as accidental overdose by the review committee giving a total of 36 overdoses	In this primary study by Metz et al. 2016, the following candidate factors was identified as potentially playing a role in maternal poisoning deaths; • prescription opioids were the main drug involved • a high proportion had prior psychiatric illness diagnosed, mainly depression • have 2 or more drugs present on toxicology • social stressors such as unemployment, being a victim of violence, homeless, being single, divorced or widowed
Szymanski et al. 2016	United States	Suicidal Drug Overdose in New Mexico:	Retrospective secondary data analysis of suicidal overdoses (2008–2012)	342 deaths (211 women, 131 men)	In this primary study by Szymanski et al. 2016, the following candidate factors were identified as playing a potential role in suicide drug poisoning deaths; women tended to:

			using medical investigator data		• be older than their male counterparts with a mean age of 48.5 years for females, and 45.7 years for males • represent the majority of suicide poisoning deaths • represent the majority with chronic pain reported as a stressor • have opioid narcotics present on toxicology • have more than one drug involving in their death, especially in women with chronic pain • have a higher increase in the number of deaths over the reporting period compared to men
Gladstone et al. 2016	Canada	Prescription opioid-related deaths in British Columbia, Canada	Retrospective secondary data analysis of mortality data obtained from the vital statistics agency and demographic data from universal public health insurance plan.	3775 drug-poisoning related deaths 2004-2013 of which 1674 involved px opioids (558 Women , 1116 men)	In this primary study by Gladstone et al. 2016, the following candidate factors were identified as playing a role in prescription opioid drug poisoning deaths; women tended to: • mainly died of unintentional opioid poisoning deaths • have a high proportion of opioid poisoning deaths linked to suicide compared to men
Hayashi et al. 2016	Canada	Death Among Injection Drug Users in Vancouver, Canada	Retrospective secondary data analysis of data from cohort studies linked to British Columbia Vital Statistics Agency	2,317 deaths 1996-2011 (794 women, 1,523 men) of which 120 were due to overdoses (38 women, 82 men).	In this primary study by Hayashi et al. 2016, the following candidate factor was identified as playing a role in drug poisoning deaths among women who inject drugs; • Sex-specific interventions are required to reduce all deaths including drug poisoning deaths
Groot et al. 2016	Canada	Drug Toxicity Deaths after Release prison in Ontario, Canada 2006-2013: Review of Coroner's Cases	Retrospective secondary data analysis coroners case files matched with prison records	702 deaths (113 women, 589 men)	In this primary study by Groot et al. 2016, the following candidate factor was identified as playing a role in poisoning deaths post release from prison; women tended to: • have the highest deaths rate in the age group 25-29 years
Gao et al. 2016	Scotland	Methadone-specific deaths in Scotland’s	Retrospective secondary data analysis of death-	760 drug-related deaths (225 women, 535 men)	In this primary study by Gao et al. 2016, the following candidate factors were identified as playing a potential role in poisoning deaths involving methadone among women who were prescribed methadone; women tended to:

		methadone-prescription clients between 2009 and 2013	records methadone prescriptions		• experience a much lower poisoning death rate than their male counterparts at younger ages but, progressively, this advantage weakens beyond 35 years of age • have a risk-factor for QTc prolongation and methadone also effects the electrical conductivity of the heart muscle putting women at high risk of sudden cardiac death
Austin et al. 2017	United States	Self-inflicted and unintentional drug overdose deaths in North Carolina in 2012	Retrospective secondary data analysis linking data between 3 databases	1221 deaths (510 women, 711 men)	In this primary study by Austin et al. 2017, the following candidate factors were identified as playing a potential role in poisoning deaths; women tended to: • represent the majority of intentional drug poisoning deaths, which mainly involve prescription opioids followed by antidepressant drugs
Roxburgh et al. 2017	Australia	Trends in heroin and pharmaceutical opioid overdose deaths in Australia 2001-2012	Retrospective secondary data analysis of data from the National Coronial Information System	8547 deaths of which approx. 32% were women	In this primary study by Roxburgh et al. 2011, the following candidate factor was identified as playing a potential role in opioid poisoning deaths; women tended to: • have an increased rate of deaths due to pharmaceutical opioid
Bukten et al. 2017	Norway	To estimate and compare overdose death rates at time intervals after prison release and to estimate the effect on overdose death rates over calendar time 1 January 2000 to 31 December 2014	15-year prospective cohort study	493 overdose deaths in total, no breakdown of number of deaths by sex given	In this primary study by Bukten et al. 2017, the following candidate factor was identified as playing a role in poisoning deaths; women tended to: • have an increased risk of poisoning death within the first 6 months post prison release
Pizzicato et al. 2018	United States	Overdose mortality following release prison in	Retrospective secondary data analysis linking prison records with data from the Medical Examiner's Office	837 overdose deaths (194 women, 643 men)	In this primary study by Pizzicato et al. 2018, the following candidate factor was identified as playing a role in poisoning deaths; women tended to: • be at an increased risk of poisoning death if they have been in prison compared to women who had not been in prison

		Philadelphia, 2010-2016			
Nechuta et al. 2018	United States	The association of sociodemographic factors and prescribing patterns with opioid overdose deaths	Retrospective secondary data analysis linking death certificates data with the controlled substance monitoring database data	5483 deaths (2393 women, 3090 men)	In this primary study by Nechuta et al. 2018, the following candidate factors were identified as playing a potential role in poisoning deaths; women tended to: • be associated with increased odds of prescription opioid poisoning death with the highest number of prescription opioid poisoning deaths in the age group 45-54 years • have increased odds of death involving an opioid and benzodiazepine combined
Jalal et al. 2018	United States	Drug overdose in the United States from 1979-2016	Retrospective secondary data analysis study involving review of national vital statistics	599,255 unintentional drug poisonings (higher % men, but no specific breakdown given)	In this primary study by Jalal et al. 2018, the following candidate factors were identified as playing a potential role in poisoning deaths; women tended to: • have prescription opioids and unspecified drugs involved in drug poisoning deaths • be older than their male peers who died of drug poisoning deaths
Gomes et al. 2018	Canada	Prescribed and non-prescribed opioids and related deaths in Ontario, Canada 2013-2016	Retrospective secondary data analysis of data from coronial investigations, health insurance plans data, the Narcotics Monitoring System and hospital attendance data	2833 deaths (922 women, 1911 men)	In this primary study by Gomes et al. 2018, the following candidate factor was identified as playing a role in opioid drug poisoning deaths; women tended to: • be more likely to have had an active opioid prescription at time of death
Scholl et al. 2019	United States	Overview of drug overdose deaths in US 2013-2017: mainly focused on opioid drugs	Retrospective secondary data analysis involving National Vital Statistics	89849 deaths during 2016 and 2017 combined (29014 women, 60835 men)	In this primary study by Scholl et al. 2019, the following candidate factors were identified as playing a potential role in poisoning deaths; women tended to: • have the highest number of poisoning deaths involving all types of opioids in the 25-44 years age group • poisoning deaths involving prescription opioids were highest in the age group 45-64 years
VanHouten et al. 2019	United States	Drug Overdose Deaths Among Women Aged 30–64 Years —	Retrospective secondary data analysis involving National Vital Statistics	Large sample (from 4314 deaths in 1999 to 18110 deaths in 2017 among women	In this primary study by VanHouten et al. 2019, the following candidate factors were identified as playing a potential role in poisoning deaths from 1999 to 2017; for women: • the highest increase in rates of poisoning deaths was in the age group 55-64

		United States, 1999–2017			• there was an increase in the rates of poisoning deaths involving antidepressants with the highest increase in the age group 60-64 years • there was an increase in poisoning deaths involving benzodiazepines similar increased rates in every age group • there was an increase in poisoning deaths involving cocaine with similar increased rates in every age group • there was an increase in the rates of poisoning deaths involving heroin with the highest increase in the age group 30-34 years • there was an increase in the rates of poisoning deaths involving prescription opioid, with the highest increase in the age group 55-64 years • there was an increase in the rates of poisoning deaths involving synthetic opioids, with the highest increase in the age group 30-34 years • overall, the average age at death has increased by almost 3 years over the study period

Appendix 2.3 Supplementary Table B Characteristics of Secondary Research Included (*n* = 11)

Author and year	Country	Focus of study	Study type/data resource	Candidate factor(s) identified as associated with poisoning deaths among women
Centers for Disease Control and Prevention 2013	United States	Prescription Painkiller Overdoses	Technical report	In this report, the following candidate factors were identified as potentially playing a role in prescription painkiller drug poisoning deaths; women tended to: • have prescription opioids involved in their death • be aged 45 to 54 years • have high representation of non-Hispanic white, American Indian or Alaska identity • have a faster escalation from regular to problematic use • be more likely to be prescribed painkillers for treatment of chronic pain • obtaining prescriptions from multiple prescribers thus more access to drugs • have concurrent mental illness • have antidepressant drugs involving in their poisoning death
Clark et al. 2015	Europe	The gender dimension of non-medical use of prescription drugs in Europe and the Mediterranean region	Technical report	In this report of a European expert working group, the following candidate factors were identified as potentially playing a role in drug poisoning deaths involving non-medical use of prescription drugs; women tended to: • be prescribed psychotropic drugs more than men • have psychotropic drugs especially antidepressants involved in their poisoning death • suffer from concurrent mental illness • have shorter 'drug user life expectancy'. Compared to men, they experience quicker escalation from regular to problematic substance use onto drug poisoning death • be victims of violence or sexual abuse
Iwanicki et al. 2015	United States	Prescription opioid death rates	Conference abstract	In this abstract, the following candidate factors were identified as potentially playing a role in prescription opioid drug poisoning deaths; women tended to: • have a higher rate of prescription opioid poisoning deaths compared to men • be dispensed more prescription opioids thus higher death rate of opioid poisoning deaths among women may be due to greater drug availability
Office on Women's Health 2017	United States	Opioid Use, Misuse, and Overdose in Women	Technical report	In this report by the Office on Women's Health 2017, the following candidate factors were identified as potentially playing a role in deaths by drug poisoning among women: women in the studies reviewed tended to:

				• have shorter 'drug user life expectancy'. Compared to men, they faster escalation from regular to problematic substance use to drug poisoning death • experience barriers to engaging with drug treatment services • have high rates of both prescription opioids and/or heroin drug poisoning deaths • use multiple drugs by getting prescriptions from multiple prescribers • have psychological and emotional distress identified as risk factors for hazardous prescription opioid use • have higher rates of chronic pain and sleep deprivation compared to men • be more prominent in rural areas • be victims of domestic violence or sexual abuse
Taylor 2016	England	Understanding and preventing drug-related deaths. The report of a national expert working group to investigate drug-related deaths in England	Technical report	In this report of a national expert working group, the following candidate factors were identified as potentially playing a role in deaths by drug poisoning; women tended to: • have an increased risk of drug poisoning death linked to an increase in age • have a correlation between drug poisoning death and being divorced
ACMD 2016	United Kingdom	Reducing Opioid-Related Deaths in the UK	Scoping review	In this scoping review by the ACMD 2016 the following candidate factors were identified as potentially playing a role in deaths by drug poisoning; women in the studies reviewed tended to: • have an increased risk of drug poisoning death linked to an increase in age • account for an increasing proportion of opioid poisoning deaths
Department of Health 2017	Ireland	Reducing harm, supporting recovery: a health-led response to drug and alcohol use in Ireland 2017—2025.	Technical report (Government strategy to tackle substance misuse)	In this Government strategy report the following candidate factors were identified as potentially playing a role in the deaths by drug poisoning; women tended to: • experience barriers to engaging with drug treatment services • be victims of domestic violence • possibly have experienced mental illness
Diamond 2018	United States	Opioid Deaths Among Women Not Getting the	Editorial article	In this report, the following candidate factors were identified as potentially playing a role in opioid drug poisoning deaths; women tended to: • be aged 45 to 54 years

		Attention They Warrant		• have prescription opioids involved in their death • be less likely than men to receive naloxone, a drug that can reverse an opioid poisoning • Be more likely to be victims of physical or sexual abuse including childhood adversity • have concurrent mental illness especially mood and anxiety disorders • be more likely to have substance use disorder than their male counterparts in prison • require more attention to issues of mental health, trauma, pregnancy, and parenting in treatment planning • develop dependence on various substances faster and at smaller amounts
Tweed et al. 2018	Scotland	Why are drug-related deaths among women increasing in Scotland? A scoping of possible explanations 2000-2016	A scoping review	In this scoping review by Tweed et al. 2018 the following candidate factors were identified as potentially playing a role in deaths by drug poisoning among women; women in the studies reviewed tended to: • be aged 35-65 years with and increased risk linked to an increase in age • have prescription opioids involved in their death • have antidepressants involved in their death • have 2 or more drugs involved in their death • suffer from concurrent mental illness • have their drug poisoning death linked to suicide • be affected more than men by adverse impacts of welfare reform • have experienced trauma and adversity • increased prevalence of physical illness • experience barriers to engaging with drug treatment services
Barnsdale et al. 2018	Scotland	The National Drug-Related Deaths Database (Scotland) Report: Analysis of Deaths occurring in 2015 and 2016	Technical report	In this report by Barnsdale et al. 2018 the following candidate factors were identified as potentially playing a role in deaths by drug poisoning, women tended to: • be aged 35-44 years • have a high rate of drug poisoning death linked to suicide • have a history of injecting drugs • have been in receipt of OST • have increased prevalence of physical illness including chronic pain • suffer from concurrent mental illness • be victims of domestic violence or sexual abuse • have antidepressants involved in their death • have prescription opioids involved in their death

UNODC World Drug Report 2018	United Nations	Women and drugs: Drug use, drug supply and their consequences	Technical report	In this report by the United Nations Office on Drugs and Crime, the following candidate factors were identified as potentially playing a role in drug poisoning deaths among women; women in the studies and data reviewed, tended to: • have a faster escalation from regular to problematic substance use and to drug poisoning death • have opioids involved in their death • experience barriers to engaging with drug treatment services • be victims of violence or sexual abuse including childhood adversity • be used as drug 'mules' • have a higher proportion of imprisonment for drug-related offences compared to men • suffer from concurrent mental illness • have high non-medical use of tranquillizers • report having chronic pain • be victims of social inequalities and lack of social and economic resources

Appendix 2.4 Supplementary Table C MEDLINE search strategy

Date	**Searched on 02/05/2018 with alerts included up to 02/11/2019**
	Search MeSH terms for mortality, fatal outcome (comes under the MeSH term mortality) and cause of death
#1	Search ("Mortality/drug effects"[Majr:noexp] OR "Mortality/statistics and numerical data"[Majr:noexp] OR "Mortality/trends"[Majr:noexp])
	Search key words in the title abstract
#2	Search (death[title/Abstract] OR deaths[Title/Abstract])
	Combine search #1 OR #2
#3 (#1 OR #2)	("Mortality/drug effects"[Majr:noexp] OR "Mortality/statistics and numerical data"[Majr:noexp] OR "Mortality/trends"[Majr:noexp] OR death[title/Abstract] OR deaths[Title/Abstract])
	Search Mesh terms Substance disorders
#4	Search ("Prescription Drug Misuse"[Mesh] OR "Drug Misuse"[Mesh]) OR ("Substance-Related Disorders"[Mesh] AND ("Substance-Related Disorders/adverse effects"[Mesh] OR "Substance-Related Disorders/analysis"[Mesh] OR "Substance-Related Disorders/blood"[Mesh] OR "Substance-Related Disorders/complications"[Mesh] OR "Substance-Related Disorders/drug effects"[Mesh] OR "Substance-Related Disorders/epidemiology"[Mesh] OR "Substance-Related Disorders/history"[Mesh] OR "Substance-Related Disorders/legislation and jurisprudence"[Mesh] OR "Substance-Related Disorders/metabolism"[Mesh] OR "Substance-Related Disorders/mortality"[Mesh] OR "Substance-Related Disorders/pathology"[Mesh] OR "Substance-Related Disorders/pharmacology"[Mesh] OR "Substance-Related Disorders/prevention and control"[Mesh] OR "Substance-Related Disorders/standards"[Mesh] OR "Substance-Related Disorders/statistics and numerical data"[Mesh] OR "Substance-Related Disorders/toxicity"[Mesh] OR "Substance-Related Disorders/trends"[Mesh] OR "Substance-Related Disorders/urine"[Mesh]))
	Combine search #4 AND search #3

#5 (#4 AND #3)	Search ("Prescription Drug Misuse"[Mesh] OR "Drug Misuse"[Mesh]) OR ("Substance-Related Disorders"[Mesh] AND ("Substance-Related Disorders/adverse effects"[Mesh] OR "Substance-Related Disorders/analysis"[Mesh] OR "Substance-Related Disorders/blood"[Mesh] OR "Substance-Related Disorders/complications"[Mesh] OR "Substance-Related Disorders/drug effects"[Mesh] OR "Substance-Related Disorders/epidemiology"[Mesh] OR "Substance-Related Disorders/history"[Mesh] OR "Substance-Related Disorders/legislation and jurisprudence"[Mesh] OR "Substance-Related Disorders/metabolism"[Mesh] OR "Substance-Related Disorders/mortality"[Mesh] OR "Substance-Related Disorders/pathology"[Mesh] OR "Substance-Related Disorders/pharmacology"[Mesh] OR "Substance-Related Disorders/prevention and control"[Mesh] OR "Substance-Related Disorders/standards"[Mesh] OR "Substance-Related Disorders/statistics and numerical data"[Mesh] OR "Substance-Related Disorders/toxicity"[Mesh] OR "Substance-Related Disorders/trends"[Mesh] OR "Substance-Related Disorders/urine"[Mesh])) AND ("Mortality/drug effects"[Majr:noexp] OR "Mortality/statistics and numerical data"[Majr:noexp] OR "Mortality/trends"[Majr:noexp] OR death[title/Abstract] OR deaths[Title/Abstract])
	Search MeSH terms and key words for exclusion criteria
#6	Search ("ethanol"[MeSH Terms] OR "ethanol"[All Fields] OR "alcohol"[All Fields] OR "alcohols"[MeSH Terms] OR "alcohols"[All Fields]) OR ("alcoholism"[MeSH Terms] OR "alcoholism"[All Fields])) NOT ("Clinical Trial"[Publication Type] OR "Controlled Clinical Trial"[Publication Type] OR "Clinical Trial, Phase IV"[Publication Type] OR "Clinical Trial, Phase III"[Publication Type] OR "Clinical Trial, Phase II"[Publication Type] OR "Clinical Trial, Phase I"[Publication Type] OR "Randomized Controlled Trial"[Publication Type]) NOT "Medical Errors"[Mesh])
	Combine #5and NOT #6
#7 (#5 NOT #6)	Search ("Prescription Drug Misuse"[Mesh] OR "Drug Misuse"[Mesh]) OR ("Substance-Related Disorders"[Mesh] AND ("Substance-Related Disorders/adverse effects"[Mesh] OR "Substance-Related Disorders/analysis"[Mesh] OR "Substance-Related Disorders/blood"[Mesh] OR "Substance-Related Disorders/complications"[Mesh] OR "Substance-Related Disorders/drug effects"[Mesh] OR "Substance-Related Disorders/epidemiology"[Mesh] OR "Substance-Related Disorders/history"[Mesh] OR "Substance-Related Disorders/legislation and jurisprudence"[Mesh] OR "Substance-Related Disorders/metabolism"[Mesh] OR "Substance-Related Disorders/mortality"[Mesh] OR "Substance-Related Disorders/pathology"[Mesh] OR "Substance-Related Disorders/pharmacology"[Mesh] OR "Substance-Related Disorders/prevention and control"[Mesh] OR "Substance-Related Disorders/standards"[Mesh] OR "Substance-Related Disorders/statistics and numerical data"[Mesh] OR "Substance-Related Disorders/toxicity"[Mesh] OR "Substance-Related Disorders/trends"[Mesh] OR "Substance-Related Disorders/urine"[Mesh])) AND ("Mortality/drug effects"[Majr:noexp] OR "Mortality/statistics and numerical data"[Majr:noexp] OR "Mortality/trends"[Majr:noexp] OR death[title/Abstract] OR deaths[Title/Abstract]) NOT (("ethanol"[MeSH Terms] OR "ethanol"[All Fields] OR "alcohol"[All

	Fields] OR "alcohols"[MeSH Terms] OR "alcohols"[All Fields]) OR ("alcoholism"[MeSH Terms] OR "alcoholism"[All Fields])) NOT ("Clinical Trial"[Publication Type] OR "Controlled Clinical Trial"[Publication Type] OR "Clinical Trial, Phase IV"[Publication Type] OR "Clinical Trial, Phase III"[Publication Type] OR "Clinical Trial, Phase II"[Publication Type] OR "Clinical Trial, Phase I"[Publication Type] OR "Randomized Controlled Trial"[Publication Type]) NOT "Medical Errors"[Mesh])
	Apply Filters
Filters	last 20 years[PDat] AND Humans[Mesh]
	Final search string with filters
#8	Search ("Prescription Drug Misuse"[Mesh] OR "Drug Misuse"[Mesh]) OR ("Substance-Related Disorders"[Mesh] AND ("Substance-Related Disorders/adverse effects"[Mesh] OR "Substance-Related Disorders/analysis"[Mesh] OR "Substance-Related Disorders/blood"[Mesh] OR "Substance-Related Disorders/complications"[Mesh] OR "Substance-Related Disorders/drug effects"[Mesh] OR "Substance-Related Disorders/epidemiology"[Mesh] OR "Substance-Related Disorders/history"[Mesh] OR "Substance-Related Disorders/legislation and jurisprudence"[Mesh] OR "Substance-Related Disorders/metabolism"[Mesh] OR "Substance-Related Disorders/mortality"[Mesh] OR "Substance-Related Disorders/pathology"[Mesh] OR "Substance-Related Disorders/pharmacology"[Mesh] OR "Substance-Related Disorders/prevention and control"[Mesh] OR "Substance-Related Disorders/standards"[Mesh] OR "Substance-Related Disorders/statistics and numerical data"[Mesh] OR "Substance-Related Disorders/toxicity"[Mesh] OR "Substance-Related Disorders/trends"[Mesh] OR "Substance-Related Disorders/urine"[Mesh])) AND ("Mortality/drug effects"[Majr:noexp] OR "Mortality/statistics and numerical data"[Majr:noexp] OR "Mortality/trends"[Majr:noexp] OR death[title/Abstract] OR deaths[Title/Abstract]) NOT (("ethanol"[MeSH Terms] OR "ethanol"[All Fields] OR "alcohol"[All Fields] OR "alcohols"[MeSH Terms] OR "alcohols"[All Fields]) OR ("alcoholism"[MeSH Terms] OR "alcoholism"[All Fields])) NOT ("Clinical Trial"[Publication Type] OR "Controlled Clinical Trial"[Publication Type] OR "Clinical Trial, Phase IV"[Publication Type] OR "Clinical Trial, Phase III"[Publication Type] OR "Clinical Trial, Phase II"[Publication Type] OR "Clinical Trial, Phase I"[Publication Type] OR "Randomized Controlled Trial"[Publication Type] NOT "Medical Errors"[Mesh] AND "last 20 years"[PDat] AND Humans[Mesh])

Appendix 2.5 Lisbon addiction conference poster - Drug poisoning deaths among women: a scoping review

Drug poisoning deaths among women: a scoping review

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No conflict of interest to disclose by any of the authors

Background

Drug poisoning deaths among women have increased at a higher rate relative to men[1,2], and remain a challenge for public health policy.

Although biological, social and psychological differences between sexes may impact on drug poisoning deaths, few studies have included detailed sex specific analysis.

Objectives

To obtain a broad knowledge in the area of drug poisoning deaths among women by charting the extent, range and nature of evidence related to this topic[3] and to identify further research, policy and practice needs in this area.

The outcome should guide further research and policy implications with the aim to help decrease the upward trend of drug poisoning deaths among women.

Definitions

- Drugs: includes both legal pharmaceutical drugs and illegal (to manufacture, sell or consume) drugs
- Poisoning death: includes all manners of death where the cause of death is directly due to the toxic effect of one or more drug(s) on the body, with the exclusion of deaths due to medical misadventure
- Medical misadventure: an accidental death caused by a person while performing a legal act without negligence or intent to harm

Methodological Framework

This scoping review used Arksey & O'Malley's (2005) 5 stage framework with additional optional 6th stage 'consultation exercise'[3]

Identify research question
- What is already known about drug poisoning deaths among women?
- What methodologies were used?
- Are there knowledge gaps in this research area?

Identify relevant studies
- Search strategy: relevant key words & assistance of information officer
- Searched Medline, CINAHL, EMBASE and Web of Science (n= 4878)
- Supplemented by grey literature, updates from specialised library, cited references and conference/event attendance (n= 33)
- Total = 4637 items (4911 – 274 duplicates)
- Limited to English and last 20 years of publications (1998-2018) plus weekly alert updates up to August 2019

Study selection
- Inclusion criteria: detailed information on poisoning deaths among women
- Two independent reviewers
- Screened 4637 titles/abstracts: PRISMA flow chart
- 235 full text papers
- Final selection included 64 items

Charting data
- Key information charted from 235 full text papers
- Extra data charted from 64 final papers selected, included; drugs involved, concepts linked to poisoning deaths among women, gaps in knowledge

Collating & summary

Involved collating and summarising the following;
- Emerging themes
- Main areas of research interest
- Research methods used
- Geographic coverage of the included literature
- Gaps in research identified
- Policy implications

Consultation exercise
- Consultation with national stakeholders through the National Drug-Related Deaths Index Steering Committee in Ireland
- Consultation with experts in the EMCDDA

Results

Emerging themes

- Opioids: the main drugs involved were prescription opioids and/or opioids in combination with other drugs
- 40+yrs: Mainly involved middle-aged women: 40-64 years of age
- Substance misuse treatment in general is not sex specific. In addition, barriers to accessing treatment exist for women
- Higher rates of mental ill health among women relative to men, mainly anxiety and depression
- Suicide by poisoning more prominent in women
- Psychotropic medicines, especially antidepressants more prominent in poisoning deaths among women
- Influence of biological differences between sexes: includes pharmacokinetics and pharmacodynamics
- Involvement of polydrugs especially CNS depressant drugs

Type of evidence

- The majority of papers contained epidemiological trend data
- Qualitative data mainly came from grey literature
- The majority of papers originated in the EU

Gaps in research/Policy implications

Areas identified as risk factors but lack extensive research;
- Imprisonment
- Victims of violence
- Alcohol-related disorders
- Chronic pain
- Cumulative social welfare payments
- Misuse of prescription medications especially psychotropic medications

Policy/practice implications;
- Expand availability of naloxone especially to at risk groups
- Gender sensitive treatment to be offered
- More advanced addiction training required
- Monitor for substance misuse and mental ill health for clients prescribed opioids and/or antidepressants
- Prescribers and users need to be more aware of the danger of polydrug use
- ECG monitoring for older client receiving methadone

Conclusion

In-depth research evidence on drug poisoning deaths among women is lacking. The majority of published research was ***not sex specific.*** Data, in the main, was dominated by mortality among men, therefore, may mask identifying potential risk factors for women. If policies and practices aimed at ***prevention*** of drug poisoning deaths in women, are to be ***meaningful***, it is important to ***investigate risk factors specifically related to women.***

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Appendix 3.1 Drugnet Ireland article: Trends in drug poisoning deaths, by sex, in Ireland: a repeated cross-sectional study, 2004–2017

Introduction

Drug poisoning (overdose) deaths are a leading cause of avoidable death with rates increasing globally. According to the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA), the mortality rate due to drug poisoning in the European Union in 2019 is estimated at 14.8 deaths per million population aged 15–64 years, with over three-quarters (77%) of these deaths among men.[1] 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. A 2021 publication examined differences by sex in the rates of overall drug poisoning deaths and deaths involving specific drugs implicated in drug poisoning deaths in Ireland between 2004 and 2017.[2]

Methods

Data for this study were extracted from the National Drug-Related Deaths Index (NDRDI) and the Health Service Executive's Primary Care Reimbursement Service (PCRS). The NDRDI's definition of a poisoning death is a death directly due to the toxic effect of one or more substances on the body. Joinpoint Regression Program was used to examine any changes in trends in age-standardised rates (ASR) from 2004 to 2017, expressed as annual percentage changes, with a summary of the overall trend expressed as an average annual percentage change (AAPC). The relationship between the ASR of drug poisoning deaths and prescription data for benzodiazepines and antidepressants was examined using linear regression. Analyses were stratified by sex.

Results

There has been an increase in the ASR of drug poisoning deaths in Ireland, from 6.86 per 100,000 in 2004 to 8.08 per 100,000 in 2017. This increase is mainly driven by deaths among men. For men, drug poisoning deaths involving cocaine

(AAPC 7.7% [(95% CI: 2.2–13.6]); benzodiazepines (AAPC 7.2% [(95% CI: 2.9–11.6]); antidepressants (AAPC 6.1% [(95% CI: 2.4–10.0]); and prescription opioids (AAPC 3.5% [(95% CI: 1.6–5.5]) increased significantly between 2004 and 2017. For women, drug poisoning deaths involving antidepressants (AAPC 4.2% [(95% CI: 0.2–8.3]); benzodiazepines (AAPC 3.3% [(95% CI: 0.1–6.5]); and prescription opioids (AAPC 3.0% [(95% CI: 0.7–5.3]) increased significantly between 2004 and 2017, with a significant increase in drug poisoning deaths involving cocaine (albeit from a low baseline number of deaths), observed in the latter part (2011–2017) of the study period. While the ASR of drug poisoning deaths involving alcohol decreased among women (AAPC –4.0 [(95% CI: –5.8 to –2.1]), there was no significant change observed among men.

A significant increase in two or more central nervous system (CNS) depressant drugs involved in drug poisoning deaths is reported among both men (AAPC 5.6% [95% CI: 2.4–8.8]) and women (AAPC 4.0% [95% CI: 1.1–6.9]).

Conclusions

The authors conclude that there was an increase in overall drug poisoning deaths in Ireland from 2004 to 2017. The increasing trend of two or more CNS depressant drugs implicated in drug poisoning deaths, especially the more recent significant increase among women, is of concern. The findings from this study highlight the need for an increased understanding among prescribers, people who use drugs, and policymakers of the physiological differences between men and women, how this affects drug activity in the body, and the associated risks with consumption of multiple CNS depressant drugs.

A significant decrease in drug poisoning deaths involving alcohol was reported for women. However, no significant change was reported for deaths involving alcohol among men. The authors highlight that alcohol is a CNS depressant and suggest that prescribers should assess for and advise on alcohol use when prescribing CNS depressant drugs.

Benzodiazepines were the most common drug group in deaths involving two or more CNS depressants. The decreasing rate of benzodiazepines dispensed through the PCRS appears to correspond with the introduction of stricter prescribing regulations. Given the increased availability of illicit benzodiazepines,[3] this change in prescribing regulations may have partially resulted in an increased use of high potent

illicit benzodiazepines. The authors state that advocates for people who use drugs should be consulted on and contribute to policy decisions around drug use. In addition, increased focus on treatment provision for misuse of benzodiazepines should be considered. The authors suggest that 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.

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Appendix 4.1 Supplementary Table D: Pearson correlation coefficient between the main other drugs present on toxicology and covariates ‘a history of opioid misuse’ and ‘in receipt of treatment for problematic drug use’

	1	2	3	4	5	6	7
1. History of opioid misuse	1						
2. In receipt of treatment for problematic drug use	.496**	1					
3. Number of other CNS depressants on toxicology	.486**	.287**	1				
4. Antidepressants on toxicology	-.074	.028	-.019	1			
5. Z drugs on toxicology	.021	.151	-.099	.077	1		
6. Antipsychotics on toxicology	-.158*	.044	-229**	.028	.024	1	
7. Cocaine on toxicology	-.308**	-.275**	-.188*	-.069	-.113	.058	1

*. Correlation is significant at the 0.05 level (2-tailed).

**. Correlation is significant at the 0.01 level (2-tailed).

Appendix 4.2 Drugnet Ireland article: Has an increase in the dispensing of pregabalin influenced poisoning deaths in Ireland?

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Introduction

Deaths caused by the toxic effect of drugs (poisoning deaths) are preventable and good clinical practice with supporting legislation can help prevent such deaths. Irish data on poisoning deaths shows an increase in direct pregabalin-related poisoning deaths from the years 2013 to 2016.[1] Of note, pregabalin, a prescribed medicine used in the treatment of several medical conditions including epilepsy, neuropathic pain, and generalised anxiety disorder, has only been included in the routine postmortem toxicology screen by The State Laboratory since 2013.

Following its introduction in 2004, international evidence found an increase in the rates of pregabalin prescriptions.[2,3,4] Fatal overdoses related to pregabalin have been reported and are almost always in combination with other drugs.[5,6] The aim of this study was to examine whether the increase in dispensing of pregabalin has impacted on poisoning deaths in Ireland between 2013 and 2016.

Methods

Prescription data was retrieved from the HSE Primary Care Reimbursement Service (PCRS) annual reports,[7] which records payment and prescription frequency for several services in Ireland. These services include; the General Medical Services (GMS) which in 2014 related to 43% of the general population,[8] and services which cover the remainder of the population; data on drugs provided through the Long Term Illness Scheme (LTI) which covers free drugs for the treatment of specific long term illnesses and data on repayments through the Drug Payment Scheme (DPS) which reimburses any citizen who pays more than a set amount monthly for medicines.

Data on all poisoning deaths for years of death 2013 to 2016 where there was a positive toxicology for pregabalin were extracted from the NDRDI. The NDRDI is an epidemiological census which records all poisoning deaths by drug(s) and/or alcohol. It also records non-poisonings deaths among persons who have a history of drug and/or alcohol dependence or misuse of drugs. The NDRDI's main data source is coronial files. All postmortem toxicological analyses included in this report were performed by The State Laboratory in Ireland. Further details on the NDRDI methodology can be found in a previous publication.[9]

Descriptive statistics are presented for the number of dispensings and deaths over time. In addition, correlational analysis using linear regression was applied to estimate the relationship between number of dispensings for pregabalin and deaths over the reported time period.

Results

For the years of death 2013 and 2016 inclusive, the NDRDI recorded a total of 1489 poisoning deaths. Pregabalin was present on toxicology reports of 240 (16%) poisoning deaths during this period, increasing from 15 (4.5%) in 2013 to 94 (26%) in 2016, indicating an upward trend (χ^2 74.626, p = <0.001) in the presence of pregabalin in poisoning deaths (Table 4.2.1). The number of dispensed pregabalin items are shown in Table 4.2.1. The numbers increased year on year (Table 4.2.1).

Table 4.2.1 PCRS Pregabalin dispensing frequency, number of poisoning deaths with a pregabalin positive toxicology and % of deaths related to PCRS dispensing BY year, 2013-2016

Year of death	2013	2014	2015	2016
Total PCRS Pregabalin items dispensed*	612641	661788	715502	755159
Breakdown of PCRS pregabalin items by scheme				
GMS	*519187*	*559421*	*608801*	*652013*
DPS	*85210*	*89183*	*89844*	*85321*
LTI	*8244*	*13184*	*16857*	*17825*
All NDRDI poisoning deaths	400	370	365	354
Pregabalin positive toxicology poisoning deaths	18	53	75	94
Pregabalin: % of deaths related to items dispensed	0.0029	0.008	0.01	0.012

*These figures do not include private pregabalin items dispensed that do not fall into these categories

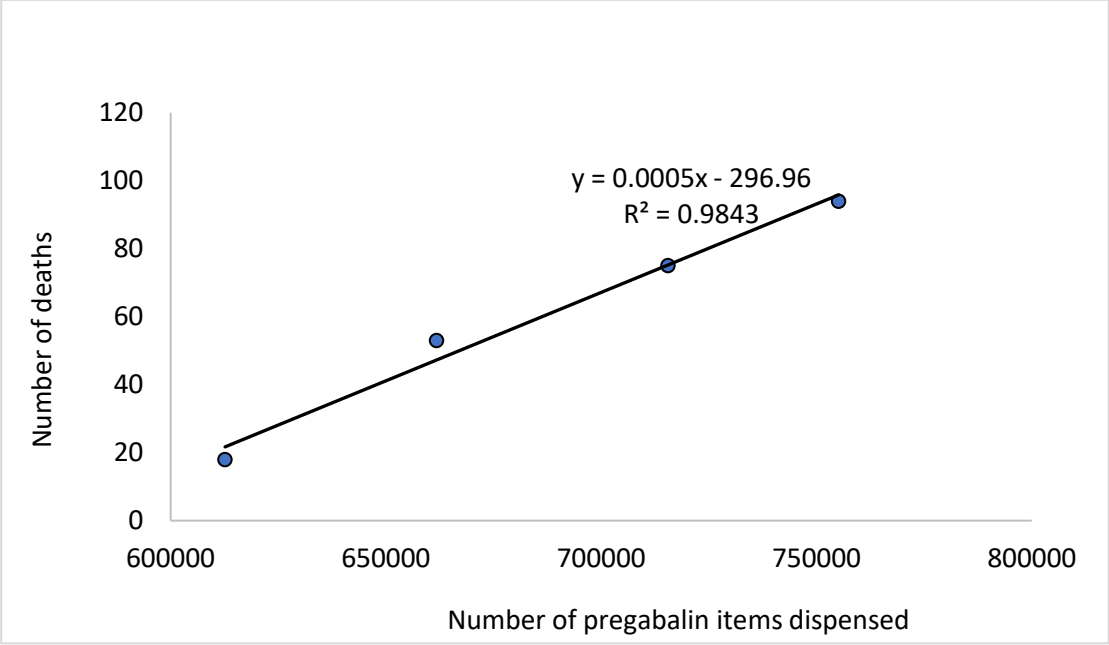

Figure 4.2.1 Relationship between the number of pregabalin items dispensed and pregabalin-positive poisoning deaths, NDRDI 2013 to 2016

Figure 4.2.1 shows a strong positive correlation was found between the number of pregabalin items dispensed through the HSE PCRS scheme and the number of poisoning deaths where pregabalin was present on toxicology over time, with a coefficient (R^2) value of 0.9843.

Discussion

This ecological study shows that pregabalin-positive poisoning deaths are increasing in line with the increased dispensing of pregabalin in Ireland. In the U.S. it has been suggested that the increase in prescribing pregabalin is related to clinicians using it outside its licensed indicated use, as an alternative to opioids for a variety of pain management.[2] From April 2019 in the United Kingdom, following recommendations from the Advisory Council on the Misuse of Drugs,[10] pregabalin (and gabapentin) is classified as a class C drug. This means that pregabalin cannot be repeat-dispensed and prescriptions will only be valid for one month. Despite acknowledgement that this will incur extra work for doctors, pharmacists and especially patients, the medical profession in general support this change.[11] Results from our study supports consideration of similar reclassification of pregabalin in Ireland. In Ireland, the HSE issued correspondence in June 2016, in relation to the

dangers associated with prescribing pregabalin;[12] however, this needs to be supported with tighter controls through legislative changes.

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Appendix 4.3 Drugnet Ireland article: A repeated cross-sectional study of factors associated with pregabalin-positive poisoning deaths in Ireland

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Introduction

Pregabalin is a prescribed medication licensed in Europe for use in the treatment of epilepsy, neuropathic pain, and generalized anxiety disorder[1]. However, the pharmacokinetic properties of pregabalin, which include its rapid absorption, fast onset of its relaxant and sedative effects and its reduced withdrawal symptoms, can lead to the potential risk of misuse. As outlined in a previous Drugnet Ireland article[2], in Ireland, rates of prescribing of pregabalin have increased in line with an increase in poisoning deaths where pregabalin was present on toxicology.

The increasing use of pregabalin and the presence of pregabalin in poisoning deaths, particularly with opioids, highlight it as a potential drug of abuse. Misuse of pregabalin has been reported; especially among people with a history of opioid misuse[3, 4], people in opioid substitution treatment[5] and people in prisons[6]. A recent Irish study, using data from the National Drug-related Deaths Index (NDRDI) examined factors associated with pregabalin-positive poisoning deaths (PPPD) between 2013 and 2016[7].

Methods

Data for this study were extracted from the NDRDI. The NDRDI's definition of a poisoning death is a death directly due to the toxic effect of one or more substances on the body; for this study pregabalin-positive poisoning deaths (PPPD) included all poisoning deaths where pregabalin was present on the toxicology report with years of death 2013 to 2016 inclusive as the observation period. Analysis included univariate and multivariate logistic regression to estimate unadjusted and adjusted odds ratios

(OR) and 95% confidence intervals (CI) for factors associated with PPPD (primary outcome) by logistic regression models for the total sample and stratified by gender.

Results

Pregabalin was present on 240 (16%) toxicology reports of 1,489 poisoning deaths: significantly rising from 15 (4.5%) in 2013 to 94 (26%) in 2016. While the total number of poisoning deaths appeared to decrease over the reporting period, there was an increase in PPPD (Table 4.3.1). Women, opioid misuse, in receipt of treatment for problem drug use and year of death (2016 vs 2013) were associated with increased odds of PPPD. Alcohol dependence was associated with reduced odds of PPPD. Analysis was then stratified by gender. For men: opioid misuse, in receipt of treatment for problem drug use, and year of death were associated with increased odds of PPPD, while alcohol dependence was associated with reduced odds of PPPD. For women: in receipt of treatment for problem drug use and year of death were associated with increased odds of PPPD.

Polydrugs were present on the toxicology reports of all PPPD (n=240). Almost all (234, 97.5%) had a positive toxicology report for other CNS depressant drugs, mainly opioids (211, 88%), followed by benzodiazepines (207, 86%) and alcohol (58, 24%). Methadone (122, 51%) was the main opioid reported in PPPD, followed by heroin (44, 18%). The odds of opioid drugs being present on toxicology reports (versus none) was 6.54 times more likely for PPPD than pregabalin negative poisoning deaths (PNPD) with the odds for women twice that for men.

Two or more other CNS depressant drugs were present in the majority (205, 85%) of PPPD toxicology reports. The odds of two or more CNS depressant drugs being present on toxicology reports (versus none) was 10.38 times more likely for PPPD compared to PNPD with the odds for women three times that for men. This is significant as pregabalin can exacerbate the side effects of CNS depressants drugs and with multiple CNS depressant drugs present in PPPD, the synergistic effect of the combination of these drugs increases the risk of death.

The odds of antidepressant drugs present on toxicology (versus none) was 5.49 times more likely for PPPD than PNPD; for antipsychotic drugs the odds ratio was 3.82; and for z drugs 2.74. The presence of cocaine on toxicology reports was not statistically significantly associated with PPPD.

Conclusions

The authors conclude that the study findings suggest inappropriate use of pregabalin among those who are known to misuse opioids and those in receipt of treatment for problematic drug use. More guidance and training for prescribers and treatment providers and the development of policies, including consideration given to scheduling pregabalin as a controlled drug, is recommended to better inform the public and medical practitioners of the potential harm due to ‘off label’ prescribing and of inappropriate use of pregabalin. Close monitoring of prescribing practices, diversion, and misuse of pregabalin, especially among those who use opioids and within the treatment setting in Ireland is urgently required. Any treatment with pregabalin should be subject to regular review with caution adhered to when considering prescribing pregabalin to women who are taking other drugs, especially CNS depressants. In Ireland the nationwide implementation of an ePrescription system would assist in this process. In addition, an ePrescription system would assist in preventing people altering prescriptions or receiving multiple private prescriptions from different medical practitioners.

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Table 4.3.1 Factors significantly associated with PPPD, 2013 to 2016 (n=1489)

	All poisoning deaths				Men	Women
			Unadjusted Model	Adjusted model	Adjusted model	Adjusted model
Factors *(reference category)*	PNPD	PPPD	Odds ratio (95% CI)	Odds ratio (95% CI)	Odds ratio (95% CI)	Odds ratio (95% CI)
Gender						
Women	356	111 (24%)	2.16 (1.63-2.86)***	2.69 (1.95-3.70)***		
Men(ref)	893	129 (13%)	1.00	1.00		
Year of death						
2013(ref)	382	18 (5%)	1.00	1.00	1.00	1.00
2014	317	53 (14%)	3.33 (2.04-6.18)***	3.62 (2.04-6.42)***	4.46 (2.00-10.05)***	2.74 (1.18-6.34)*
2015	290	75 (21%)	5.49 (3.21-9.39)***	5.55 (3.20-9.66)***	5.14 (2.28-11.56)***	6.05 (2.76-13.26)***
2016	260	94 (27%)	7.67 (4.52-13.01)***	7.95 (4.58-13.79)***	11.01 (5.02-24.14)***	5.24 (2.35-11.69)***
History of alcohol dependency						
Yes	360	48 (12%)	0.62 (0.44-0.87)**	0.59 (0.41-0.85)**	0.45 (0.27-0.76)**	0.84 (0.48-1.47)
No(ref)	889	192 (18%)	1.00	1.00	1.00	1.00
History of opioid misuse						
Yes	553	160 (22%)	2.52 (1.88-3.37)***	1.74 (1.17-2.59)**	1.83 (1.09-3.08)*	1.56 (0.81-3.01)
No(ref)	696	80 (10%)	1.00	1.00	1.00	1.00
In receipt of treatment for problematic drug use						
Yes	197	89 (31%)	3.15 (2.32-4.26)***	1.95 (1.33-2.86)**	1.80 (1.10-2.95)*	2.57 (1.31-5.01)**
No(ref)	1052	151 (13%)	1.00	1.00	1.00	1.00

Adjusted model is for all predictors identified as significant in the unadjusted models. Variables significant at *** p<0.001, ** p<0.01, * p<0.05

Appendix 4.4 Supplementary Table E. Sensitivity test: Unadjusted and adjusted ORs (95% CI) of factors associated with poisoning deaths with and without pregabalin on toxicology, 2013 to 2016 with 'unknowns' recorded as system missing

	All poisoning deaths 2013-2016					Men poisoning deaths 2013-2016				Women poisoning deaths 2013-2016			
	Poisoning deaths without ('No') and with ('Yes') pregabalin on toxicology			Unadjusted Model	Adjusted model	Poisoning deaths without ('No') and with ('Yes') pregabalin on toxicology			Adjusted model	Poisoning deaths without ('No') and with ('Yes') pregabalin on toxicology			Adjusted model
Possible risk factors *(reference category)*	No	Yes	Total	Odds ratio (95% CI)	Odds ratio (95% CI)	No	Yes	Total	Odds ratio (95% CI)	No	Yes	Total	Odds ratio (95% CI)
Gender													
Women	356	111	467	2.16 (1.63-2.86)***	2.60 (1.84-3.67)***					356	111	467	
Men(ref)	893	129	1022			893	129	1022					
Year of death													
2013 (ref)	382	18	400			265	8	273		117	10	127	
2014	317	53	370	3.33 (2.04-6.18)***	3.54 (1.93-6.48)***	236	31	267	4.52 (1.91-10.73)**	81	22	103	2.54 (1.05-6.15)*
2015	290	75	365	5.49 (3.21-9.39)***	5.20 (2.88-9.38)***	207	32	239	5.16 (2.18-12.23)***	83	43	126	5.51 (2.39-12.72)***
2016	260	94	354	7.67 (4.52-13.01)***	8.47 (4.74-15.16)***	185	58	243	11.57 (5.03-26.58)***	75	36	111	5.78 (2.49-13.46)***
Age groups													
Age group ≤34yrs (ref)	389	73	462			309	44	353		80	29	109	
Age group 35-44yrs	357	95	452	1.42 (1.01-1.99)*	1.11 (0.75-1.65)	272	56	328	1.24 (0.76-2.05)	85	39	124	0.95 (0.48-1.89)
Age group 45-54yrs	237	43	280	0.97 (0.64-1.46)	0.98 (0.59-1.61)	169	22	191	1.15 (0.60-2.22)`	68	21	89	0.81 (0.36-1.81)
Age group ≥55yrs	266	29	295	0.58 (0.37-0.92)*	0.59 (0.33-1.06)	143	7	150	0.40 (0.14-1.12)	123	22	145	0.73 (0.33-1.62)
Alone at time of incident that led to deaths													
Yes	578	99	677	0.78 (0.59-1.04)		425	48	473				204	
No(ref)	578	127	705			406	75	481				224	
Unemployed													
Yes	612	151	763	1.72 (1.24-2.39)**	1.28 (0.86-1.92)	483	87	570	1.06 (0.62-1.82)	129	64	193	1.70 (0.93-3.08)
No(ref)	405	58	463			241	27	268		164	31	195	
History of alcohol dependency													
Yes	360	48	408	0.62 (0.44-0.87)**	0.65 (0.44-0.96)*	637	107	744	0.50 (0.29-0.85)*	104	26	130	0.92 (0.51-1.65)
No(ref)	889	192	1081			256	22	278		252	85	337	
History of opiate misuse													
Yes	553	160	713	2.52 (1.88-3.37)***	1.61 (1.05-2.47)**	443	94	537	1.67 (0.96-2.91)	110	66	176	1.44 (0.71-2.91)
No(ref)	696	80	776			450	35	485		246	45	291	
In receipt of treatment for problematic drug use													
Yes	197	89	286	3.15 (2.32-4.26)***	1.89 (1.25-2.84)**	148	42	190	1.65 (0.97-2.79)	49	47	96	2.53 (1.25-5.15)*
No(ref)	1052	151	1203			745	87	832		307	64	371	

Adjusted model is for all predictors identified as significant in the unadjusted models

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

Appendix 5.1 Supplementary Table. Sensitivity analysis MODEL 1: Unadjusted and adjusted ORs (95% CI) comparing characteristics and factors for coronial verdict of suicide drug poisoning deaths verses non-suicide drug poisoning deaths, overall and stratified by sex, NDRDI data 2015 to 2017 inclusive (n=1114)

	All drug poisoning deaths					Drug poisoning deaths among men					Drug poisoning deaths among women				
	Cor SDPD	NSDPD	Total	Unadjusted Model	Adjusted model	Cor SDPD	NSDPD	Total	Unadjusted Model	Adjusted model	Cor SDPD	NSDPD	Total	Unadjusted Model	Adjusted model
Sex															
Women	45	314	359	1.50 (1.00 - 2.24)*	0.85 (0.53 - 1.36)										
Men *(Ref)*	66	689	755	1.00											
Age group															
Age group ≤34yrs*(Ref)*	13	270	283	1.00		10	205	215	1.00		˜	65	68	1.00	
Age group 35-44yrs	33	315	348	2.18 (1.12 - 4.22)*	1.58 (0.75 - 3.31)	19	227	246	1.72 (0.78 - 3.78)	1.26 (0.51 - 3.12)	14	88	102	3.45 (0.95 - 12.49)	2.46 (0.61 - 9.87)
Age group 45-54yrs	21	215	236	2.03 (0.99 - 4.15)	0.77 (0.34 - 1.75)	12	154	166	1.60 (0.67 - 3.79)	0.64 (0.23 - 1.80)	9	61	70	3.20 (0.83 - 12.36)	1.48 (0.33 - 6.55)
Age group ≥55yrs	44	203	247	4.50 (2.36 - 8.58)***	1.45 (0.67 - 3.14)	25	103	128	4.98 (2.30 - 10.75)***	1.60 (0.61 - 4.23)	19	100	119	4.12 (1.17 - 14.47)*	1.57 (0.37 - 6.57)
Unemployed															
Yes	30	512	542	0.29 (0.18 - 0.45)***	0.60 (0.35 - 1.04)	19	380	399	0.26 (0.14 - 0.46)***	0.58 (0.29 - 1.16)	29	114	143	0.38 (0.18 - 0.79)**	0.81 (0.33 - 1.96)
No(Ref)	63	306	369	1.00		34	175	209	1.00		11	149	160	1.00	
Employment status unknown	18	185	203	0.47 (0.27 - 0.82)**	0.87 (0.47 - 1.63)	13	134	147	0.50 (0.25 - 0.98)*	0.93 (0.43 - 2.01)	5	51	56	0.44 (0.16 - 1.21)	0.63 (0.22 - 1.86)
Homeless Status															
Homeless	5	117	122	0.36 (0.14 - 0.89)*	1.07 (0.38 - 3.01)	5	99	104	0.49 (0.19 - 1.25)		0	18	18		
Not homeless(Ref)	106	886	992	1.00		61	590	651	1.00		45	296	341	1.00	
Single marital status (includes separated/divorced)															
Yes	73	698	771	0.63 (0.41 - 0.97)*	1.01 (0.62 - 1.66)	44	498	542	0.51 (0.29 - 0.90)*	0.75 (0.40 - 1.42)	29	200	229	0.91 (0.46 - 1.81)	
No(Ref)	35	210	245	1.00		21	122	143	1.00		14	88	102	1.00	
Marital status unknown	˜	95	98	0.19 (0.06 - 0.63)**	0.34 (0.09 - 1.25)	˜	69	70	0.08 (0.01 - 0.64)*	0.13 (0.02 - 1.06)	˜	26	28	0.48 (0.10 - 2.27)	

Ever incarcerated															
Yes	11	364	375	0.19 (0.10 - 0.37)***	0.65 (0.30 - 1.41)	7	292	299	0.16 (0.07 - 0.36)***	0.62 (0.23 - 1.67)	˜	72	76	0.33 (0.11 - 0.95)*	0.95 (0.25 - 3.66)
No(Ref)	100	639	739	1.00		59	397	456	1.00		41	242	283	1.00	
History of drug use															
Yes	27	630	657	0.19 (0.12 - 0.30)***	0.31 (0.17 - 0.56)***	14	459	473	0.14 (0.07 - 0.25)***	0.28 (0.12 - 0.66)**	13	171	184	0.34 (0.17 - 0.67)**	0.31 (0.12 - 0.80)*
No(Ref)	84	373	457	1.00		52	230	282	1.00		32	143	175	1.00	
History of alcohol dependency															
Yes	24	301	325	0.64 (0.40 - 1.03)		11	203	214	0.48 (0.25 - 0.93)*	0.40 (0.19 - 0.82)*	13	98	111	0.90 (0.45 - 1.78)	
No(Ref)	87	702	789	1.00		55	486	541	1.00		32	216	248	1.00	
Known history of previous overdose															
Yes	23	91	114	2.62 (1.58 - 4.35)***	2.30 (1.26 - 4.20)**	9	55	64	1.82 (0.86 - 3.87)		14	36	50	3.49 (1.70 - 7.17)**	2.65 (1.13 - 6.20)*
No(Ref)	88	912	1000	1.00		57	634	691	1.00		31	278	309	1.00	
In receipt of treatment for drug misuse at time of death															
Yes	6	226	232	0.20 (0.09 - 0.45)***	0.49 (0.19 - 1.24)	˜	146	148	0.12 (0.03 - 0.48)**	0.32 (0.07 - 1.50)	˜	80	84	0.29 (0.10 - 0.82)**	0.51 (0.12 - 2.15)
No(Ref)	105	777	882	1.00		64	543	607	1.00		41	234	275	1.00	
History of chronic pain															
Yes	14	47	61	2.94 (1.56 - 5.53)**	2.26 (1.10 - 4.66)*	5	22	27	2.49 (0.91 - 6.80)		9	25	34	2.89 (1.25 - 6.67)*	2.31 (0.91 - 5.85)
No(Ref)	97	956	1053	1.00		61	667	728	1.00		36	289	325	1.00	
Mention of mental ill health															
Yes	92	441	533	6.17 (3.71 - 10.27)***	5.34 (3.08 - 9.27)***	51	268	319	5.34 (2.94 - 9.69)***	5.33 (2.78 - 10.20)***	˜	210	214	8.35 (2.92 - 23.88)***	7.10 (2.37 - 21.28)***
No(Ref)	19	562	581	1.00		15	421	436	1.00		41	104	145	1.00	
Polydrugs involved in death															
Yes	55	623	678	0.60 (0.40 - 0.89)*	0.68 (0.43 - 1.09)	29	412	441	0.53 (0.32 - 0.88)*	0.86 (0.47 - 1.59)	26	211	237	0.67 (0.35 - 1.26)	
No(Ref)	56	380	436	1.00		37	277	314	1.00		19	103	122	1.00	

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

˜ = value less than 5

Appendix 5.2 Supplementary Table. Sensitivity analysis: Unadjusted and adjusted ORs (95% CI) comparing drugs implicated in coronial verdict of suicide drug poisoning deaths verses non-suicide drug poisoning deaths, overall and stratified by sex, NDRDI data 2015 to 2017 inclusive (n=1114)

	All drug poisoning deaths				Drug poisoning deaths among men				Drug poisoning deaths among women			
	Cor SDPD	NSDPD	Total	Unadjusted Model	Cor SDPD	NSDPD	Total	Unadjusted Model	Cor SDPD	NSDPD		Unadjusted Model
CNS depressants implicated in poisoning death (% of poisoning deaths)												
Yes	51	865	916	0.14 (0.09 - 0.21)***	26	590	616	0.11 (0.06 - 0.19)***	25	275	300	0.18 (0.09 - 0.35)***
No (Ref)	60	138	198	1.00	40	99	139	1.00	20	39	59	1.00
Two or more other CNS depressant drugs												
Yes	34	531	565	0.39 (0.26 - 0.60)***	14	360	374	0.25 (0.13 - 0.45)***	20	171	191	0.67 (0.36 - 1.25)
No (Ref)	77	472	549	1.00	52	329	381	1.00	25	143	168	1.00
Breakdown of CNS depressant drugs												
Prescription opioids implicated in poisoning death												
Yes	27	431	458	0.43 (0.27 0 0.67)***	10	275	285	0.27 (0.14 - 0.54)***	17	156	173	0.62 (0.32 - 1.17)
No (Ref)	84	572	656	1.00	56	414	470	1.00	28	158	186	1.00
Benzodiazepines implicated in poisoning death												
Yes	20	416	436	0.31 (0.19 - 0.51)***	9	283	292	0.23 (0.11 - 0.47)***	11	133	144	0.44 (0.22 - 0.90)*
No (Ref)	91	587	678	1.00	57	406	463	1.00	34	181	215	1.00
Z drugs implicated in poisoning death												
Yes	20	177	197	1.02 (0.61 - 1.70)	10	100	110	1.05 (0.52 - 2.13)	10	77	87	0.86 (0.41 - 1.83)
No (Ref)	91	826	917	1.00	56	589	645	1.00	35	237	272	1.00
Pregabalin implicated in poisoning death												
Yes	14	144	158	0.86 (0.48 - 1.55)	5	75	80	0.67 (0.26 - 1.72)	9	69	78	0.89 (0.41 - 1.93)
No (Ref)	97	859	956	1.00	61	614	675	1.00	36	245	281	1.00
Heroin implicated in poisoning death												
Yes	~	233	235	0.06 (0.02 - 0.25)***	~	197	199	0.08 (0.02 - 0.32)***	0	36	36	
No (Ref)	109	770	879	1.00	64	492	556	1.00	45	278	323	1.00
Alcohol implicated in poisoning death												

Yes	16	360	376	0.30 (0.17 - 0.52)***	10	251	261	0.31 (0.16 - 0.62)**	6	109	115	0.29 (0.12 - 0.71)**
No (Ref)	95	643	738	1.00	56	438	494	1.00	39	205	244	1.00
Main other drugs implicated in poisoning death												
Antidepressants												
Yes	37	224	261	1.74 (1.14 - 2.65)*	17	112	129	1.79 (0.99 - 3.22)	20	112	132	1.44 (0.77 - 2.71)
No (Ref)	74	779	853	1.00	49	577	626	1.00	25	202	227	1.00
Breakdown of antidepressants drugs†												
SSRIs												
Yes	12	98	110	1.12 (0.59 - 2.11)	˜	47	51	0.88 (0.31 - 2.53)	8	51	59	1.12 (0.49 - 2.53)
No (Ref)	99	905	1004	1.00	62	642	704	1.00	37	263	300	1.00
TCAs												
Yes	19	57	76	3.43 (1.96 - 6.01)***	9	29	38	3.59 (1.62 - 7.96)**	10	28	38	2.92 (1.31 - 6.51)**
No (Ref)	92	946	1038	1.00	57	660	717	1.00	35	286	321	1.00
Other antidepressants												
Yes	16	120	136	1.24 (0.71 - 2.18)	8	61	69	1.42 (0.65 - 3.11)	8	59	67	0.93 (0.41 - 2.11)
No (Ref)	95	883	978	1.00	58	628	686	1.00	37	264	301	1.00
Antipsychotics												
Yes	15	109	124	1.28 (0.72 - 2.29)	7	61	68	1.22 (0.54 - 2.79)	9	47	56	1.20 (0.53 - 2.73)
No (Ref)	96	894	990	1.00	59	628	687	1.00	37	266	303	1.00
Non opioid analgesics												
Yes	25	77	102	3.55 (2.14 - 5.86)***	13	46	59	3.51 (1.78 - 6.91)***	12	31	43	3.32 (1.56 - 7.08)**
No (Ref)	86	926	1012	1.00	53	643	696	1.00	33	283	316	1.00
Cocaine												
Yes	˜	137	141	0.24 (0.09 - 0.65)**	˜	103	105	0.18 (0.04 - 0.74)*	˜	34	36	0.38 (0.09 - 1.65)
No (Ref)	107	866	973	1.00	64	586	650	1.00	43	280	323	1.00

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

†Individuals may have more than one antidepressant drugs implicated in their death therefore total figures from each antidepressant drug group category may not equal to the total number of individual deaths involving antidepressants

˜ = value less than 5

Appendix 5.3: Death investigation process for drug poisoning deaths in Ireland

In Ireland, all sudden, unnatural, violent, or unexplained deaths are reported to a Coroner, who has a legal responsibility to investigate these deaths. If the Coroner concludes, based on the evidence presented, that the death is due to natural causes, then the coroner will issue a 'Coroners Certificate' which is submitted to the Register of Births, Marriages, and Deaths. A death certification can then be issued from the office of the Register (Figure 1).

For suspected drug poisoning deaths further evidence is sought (Figure 1), which includes toxicology, and the investigation proceeds to an inquest. A verdict is determined in the outcome of the inquest. A verdict of suicide is based on legal guidance surrounding the weight of evidence that a person intended to take their life 'beyond reasonable doubt', which is equivalent to the burden of proof for a criminal act, albeit suicide was decriminalised in Ireland in 1993 (Criminal Law Suicide Act (1993). As a result of this strict legal criteria, suicide drug poisoning deaths, and suicide deaths in general, are likely to be under-counted (Corcoran, P. & Arensman, E., 2010; Rochford, Dodd, & Austin, 2021).

Among other factors, key elements to determine a verdict of suicide 'beyond reasonable doubt' is the presence of a current 'death note' and the method used (Palmer et al., 2015). Given the 'the beyond reasonable doubt' burden of proof required for a suicide verdict, it is likely that a proportion of deaths classified as 'undetermined', or 'accident' include possible 'hidden' cases of suicide. For example, deaths due to poisoning, jumping, and drowning are less likely to receive a verdict of suicide than other verdicts (Palmer et al., 2015).

The definition/classification for suicide drug poisoning deaths can differ across jurisdictions. For example, national statistics on drug poisoning deaths from the UK include undetermined intent, ICD 10 code Y14, in their statistics for suicide drug poisonings (Office for National Statistics, 2021). Also in England, the House of Common's Health Committee stated that the 'beyond reasonable doubt' standard for a suicide verdict causes misclassification of deaths by suicide, leading to an underestimation of the true number of suicides and recommended that the standard of proof required for a suicide verdict should be changed from 'beyond reasonable doubt' to the 'balance of probability' (House of Commons Health Committee, 2017).

The broad definition of suicide used in this study includes all drug poisoning deaths that meet the suicide on the balance of probabilities standard, that is, it is more likely than not, based on the weight of evidence, that the deceased engaged in a deliberate act which resulted in their death and was intended to cause their death. Deaths that do not have a verdict of suicide, but where there is evidence (implicit, explicit or both) that the deceased intended to take their own life, based on the Rosenberg criteria, were included as suicide drug poisoning deaths (Rosenberg et al., 1988).

Using a broader inclusion criterion (including suicide deaths, on the balance of probabilities) provides a comprehensive overview of the characteristics of people who have died by suicide drug poisoning deaths in Ireland.

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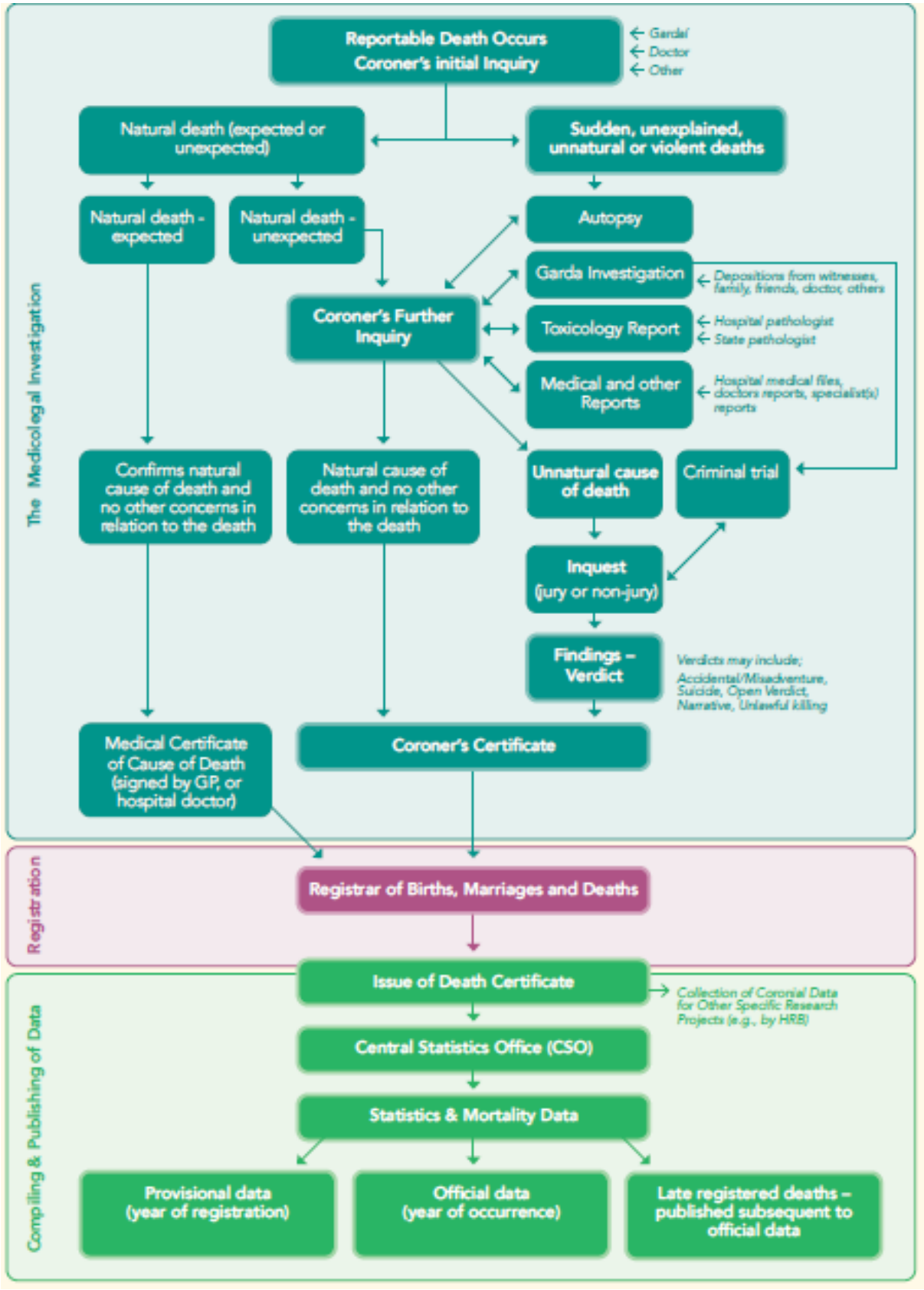

Figure 1. The Coronial Death Investigation process in Ireland. Source: National Office for Suicide Prevention (unpublished).