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Prescription drugs with potential for misuse: protocol for a multi-indicator analysis of supply, detection and the associated health burden in Ireland between 2010 and 2020

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ABSTRACT

Introduction There is an increasing concern about the misuse of prescription drugs. Misuse refers to the intentional repurposing of prescribed drugs and/or the use of illicitly sourced prescription drugs, which may be counterfeit or contaminated. Drugs with the greatest potential for misuse are prescription opioids, gabapentinoids, benzodiazepines, Z-drugs and stimulants.

Objective The aim of this study is to provide a comprehensive analysis of the supply, patterns of use and health burden associated with prescription drugs with potential for misuse (PDPM) in Ireland between 2010 and 2020. Three inter-related studies will be carried out. The first study will describe trends in supply of PDPM using law enforcement drug seizures data and national prescription records from national community and prison settings. The second study aims to estimate trends in the detection of PDPM across multiple early warning systems using national forensic toxicology data. The third study aims to quantify the health burden associated with PDPM nationally, using epidemiological indicators of drug-poisoning deaths, non-fatal intentional drug overdose presentations to hospitals and drug treatment demand.

Methods and analysis A retrospective observational study design, with repeated cross-sectional analyses, using negative binomial regression models or, where appropriate, joinpoint regression.

Ethics and dissemination The study has received approval from the RCSI Ethics Committee (REC202202020). Results will be disseminated in peer-reviewed journals, scientific and drug policy meetings and with key stakeholders via research briefs.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Multiple data sources including prescription records (community and prison setting), drug seizures data, forensic toxicology data, and epidemiological indicators of drug treatment demand, and drug poisonings will be analysed to establish robust estimates of trends in the use and harms associated with prescription drugs with potential for misuse.
⇒ All analyses will be gender sensitive as biological, social and psychological differences between men and women can impact all aspects of drug use.
⇒ Data sources are nationally representative of the Irish context, and will cover a 10-year observation period.
⇒ Strong community partnership (people who use drugs) engagement throughout the development of study protocol.
⇒ Data linkage is not possible across datasets, any examination of relationships between aggregate population trends will be limited to ecological analyses (hypothesis generating).

BACKGROUND

Misuse, or non-medical use of prescription drugs refers to the intentional repurposing of prescribed drugs outside of their intended indication, often for recreational or performance enhancement purposes.[1 2] It also refers to the use of illicitly sourced prescription drugs, potentially counterfeit, contaminated or containing adulterants.[3] Drugs identified with the greatest potential for misuse are prescription opioids, gabapentinoids, benzodiazepines, Z-drugs (eg, zopiclone, zolpidem) and psychostimulants (eg, methylphenidate).[1 4 5]

Although the European Union (EU) and the UK have identified that these drug groups are commonly prescribed in the community, often at variance with best clinical practice, most EU countries lack a systematic method for identifying and monitoring trends in the use and misuse of prescription drugs over time.[5–8] Prisons have also been identified as a high-risk setting for the misuse of both

prescription and illicit drugs. For example, tramadol, pregabalin and gabapentin have been highlighted in UK guidance to prison doctors as medications with significant abuse potential in prison settings.[9] Analysing prescribing practices in the community and prison setting will provide important insights into the supply or availability of prescription drugs with potential for misuse (PDPM) in Ireland. A 2016 report by the UK Advisory Council on the Misuse of Drugs found that the most prevalent diverted drugs are opioids, benzodiazepines and Z-drugs.[3] Analysing law-enforcement seizure data in parallel will capture illicit prescription drug supply.[3]

Drug misuse is typically characterised by the consumption of multiple substances, including illicit substances. For example, a recent UK survey estimated that 600 000 UK adults misused benzodiazepines/Z-drugs in the past year, 45% of whom also used an illicit drug during the same 12-month period.[3] However, it was not possible to determine whether the drugs were used concurrently. This complexity is challenging to monitor using prescribing or survey data alone, and requires efforts to assess other sources of data, such as forensic toxicology data.[10] At a population level, when the coverage of postmortem toxicology is high in a country, it represents a useful indicator for monitoring drug trends over time, particularly when all postmortem cases are analysed and not only those identified as drug poisoning deaths.[11] Similarly, a national database of forensic toxicology results from drivers suspected of driving while intoxicated (drugs or alcohol), allows for the identification of trends in drug use, including polydrug use, among road users.[12] To aid decisions about appropriate responses to prescription drug misuse, it is also important to consider trends among high-risk groups such as those attending drug treatment services.[13]

Finally, understanding the health burden associated with the PDPM is important. As with the question of supply and detection of potential misuse, the extent of the health burden is unknown in Ireland. Any assessment of the burden is only possible by analysing data from multiple national epidemiological data sources, such as drug treatment entrants, drug poisoning deaths and self-harm presentations to emergency departments associated with the PDPM.[10] Preliminary analysis would suggest that the health burden associated with prescription drugs is increasing in Ireland. For example, the prevalence of pregabalin in poisoning deaths, particularly with opioids, increased in Ireland between 2013 and 2016 with pregabalin detected in almost one in six poisoning deaths.[14] Similarly, there is evidence of an increase in the use of gabapentinoids in non-fatal intentional drug overdose cases in Ireland.[15] The aim of this study is to provide a comprehensive analysis of the supply, patterns of use and health burden associated with PDPM in Ireland, using data from multiple early warning systems, drug supply and epidemiological indicators. PDPM include opioids, gabapentinoids, benzodiazepines, Z-drugs and psychostimulants. The specific study objectives will be addressed using three interrelated studies:

1. Study 1: drug supply
   Describe trends in the drug supply market of illicit prescription opioids, benzodiazepines (including NPS), Z-drugs, gabapentinoids and stimulants using law enforcement drug seizure data, and prescribing trends for PDPM in primary care and prison setting, between 2010 and 2020.
2. Study 2: detection and patterns of use
   Analyse national forensic toxicology data to describe trends in the detection of PDPM across multiple early warning systems, and national drug survey data to describe patterns of use of PDPM, between 2010 and 2020.
3. Study 3: health burden associated with PDPM
   Quantify the health burden associated with the use of PDPM, using epidemiological indicators of drug-poisoning deaths, non-fatal intentional drug overdoses and drug treatment demand.

METHODS AND ANALYSIS

A retrospective observational study of Irish drug supply data, forensic toxicology data and epidemiological indicators of harms associated with PDPM, for the period 2010–2020. Repeated cross-sectional analyses will be conducted within each of the studies to estimate temporal trends.

Data sources

Law enforcement drug seizures data and prescription data

The first study will use both law enforcement drug seizures data and national prescribing data in the community and prison setting. Law enforcement drug seizures data, from Forensic Science Ireland (FSI) and the Health Products Regulatory Authority (HPRA) will be used to describe the market of illicit prescription drugs of interest between 2010 and 2020. FSI will provide data on number of drug seizures per year, by An Garda Síochána, Revenue's Customs Service officers and the Military Police, involving prescription opioids, benzodiazepines, Z-drugs, gabapentinoids, stimulants and new psychoactive substances. The HPRA will provide similar data on the number of medicinal products detained per year at port of entry, alongside detentions made following HPRA investigative actions. Aggregate-level national pharmacy claims data from the Health Service Executive-Primary Care Reimbursement Service (HSE-PCRS), specifically the General Medical Scheme (GMS), will be used to estimate prescribing trends for PDPM in people aged ≥16 years in the community setting. The GMS is the largest community drug scheme administered by the HSE-PCRS, providing free health services, including prescription medications with a small copayment. Eligibility for the GMS is based on age and means testing, covering approximately 32% of the population.[16] All prescriptions are coded using specific drug codes as well as the WHO Anatomical Therapeutic Chemical classification.[16] Monthly aggregate data on the

number of patients dispensed PDPM, total number of items dispensed and total quantity dispensed for each PDPM will be available, overall and by gender, age group and geographical region. The Irish Prison Services use a centralised electronic patient record (Prisoner Healthcare Management System), which includes records of all medicines prescribed to people while in custody in Ireland since 2011. Anonymised individual level dispensing records for prisoners aged ≥18 years, across all Irish Prisons, will be available for the study observation period. Data will include gender, age, custodial sentence (first, second, etc), duration of custodial sentence, drug prescribed with dates and dosage. Table 1 provides an overview of the drugs, which will be analysed across the three inter-related studies.

National forensic toxicology data

Forensic toxicology data from the State Laboratory (postmortem toxicology), the Medical Bureau of Road Safety (MBRS), and the HSE National Drug Treatment Centre (NDTC) Laboratory will be used for Study 2. The State Laboratory provides a forensic toxicology service to assist Coroners and the State Pathologist to investigate the causes of sudden death by analysing postmortem samples to confirm the presence or absence of ethanol, legal and illegal drugs and other toxic substances. Since 2013, all postmortem samples in the Ireland, requiring toxicology, have been submitted directly to the State Laboratory for both screening and confirmatory analysis. The Laboratory uses high-resolution liquid chromatography mass spectrometry (LC-MS) drug screening methods, with blood and urine samples screened for 167 different drugs. Anonymised individual-level data on all cases screening positive for one or more PDPM postmortem, will be used to evaluate trends in the detection rates of PDPM postmortem, both alone and in combination with other substances. Data will not be available on age and gender of the deceased.

The MBRS is a statutory body responsible for the chemical testing of intoxicants (alcohol and drugs) in drivers arrested under the Road Traffic Acts 1968–2016. The MBRS carry out routine drug testing on samples which are below a specified threshold for alcohol, or by request from the Gardaí (police). All drug driving analysis required under the Act, between 2010 and 2020, has been managed by the MBRS. Between 2010 and 2018, the laboratory used immunoassay for screening. Since 2018, screening analysis is conducted using liquid chromatography with tandem mass spectrometry (LC-MS-MS). Anonymised individual-level data, including age and gender, on all samples tested for drugs in the MBRS will be used to evaluate trends in the detection rates of PDPM among road users, both alone and in combination with other substances.

The HSE NDTC Laboratory is the largest specialist provider of urine drug screening for drug treatment services in Ireland. The NDTC Laboratory uses immunoassay screening methods for all patients attending the NDTC. Most people attend the NDTC for opioid agonist treatment (OAT) for opioid dependence. Clinical guidelines for OAT recommend at least one random drug test per month.[17] Anonymised individual-level drug screening data and age, will be used to evaluate trends in the detection rates of PDPM (at drug class level) among people attending the NDTC. Table 1 provides an overview of the drugs which are screened and/or confirmed across the three toxicology laboratories included in Study 2.

National Drug and Alcohol Survey

The National Drug and Alcohol Survey (NDAS) collects information on alcohol and tobacco consumption, and drug use among the general population in Ireland. Three nationally representative surveys have been conducted by the Health Research Board, at 4-year intervals, in Ireland since 2010 (2010, 2014 and 2019). The measures include self-reported past year use of 'sedatives and tranquilisers', opioids, and various other illicit drugs (eg, cocaine, amphetamines, ecstasy) along with sociodemographic information. Self-reported misuse of prescription drugs during the past 12 months was measured in 2019. Anonymised individual-level data, including age and gender, will be used to evaluate trends in the past year use of PDPM among the Irish population, both alone and in combination with other substances.

Epidemiological indicators of the health burden associated with PDPM

Epidemiological indicators of drug-poisoning deaths (National Drug Related Death Index (NDRDI)), non-fatal intentional drug overdoses (National Self-Harm Registry Ireland) and drug treatment demand (National Drug Treatment Reporting System (NDTRS)) will be analysed to quantify the health burden associated with the use of PDPM. The NDRDI is an epidemiological database that records all poisoning deaths by drugs and/or alcohol. It follows the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) standard protocol to collect data on drug-related deaths.[18] Drug poisoning deaths are defined as deaths directly due to the toxic effect of one or more drugs on the body, as directed by the Coroner on the certificate of death registration and/or the record of verdict. Up to six drugs implicated in drug poisoning deaths by the Coroner are included in the NDRDI. Anonymised individual-level data will be used to evaluate trends in drug poisoning deaths involving any of the PDPM listed in table 1, both alone and in combination with other substances, overall and by gender and age.

The National Self-Harm Registry Ireland, administered by the National Suicide Research Foundation, monitors hospital-treated self-harm across all 36 acute hospitals in the Ireland. Data on self-harm presentations are collected by Data Registration Officers according to Standard Operation Procedures. A maximum of five methods are recorded for presentations involving multiple methods. We will examine non-fatal intentional drug overdose presentations identified as having ICD-10 codes X60-X64.

Table 1 List of prescription drugs with potential for misuse (PDPM) and forensic toxicology data to be included in analyses

		Controlled under the Misuse of Drugs Act 2017		Prescription/Dispensing records		Class specific testing (immunoassay)		Analyte specific testing (LCMS)	
Group	Substance	Schedule 4	Schedule 2 or 3	ATC codes	GMS/Prisons	NDTC	MBRS 2010–2018	MBRS 2019–2020	State Laboratory
Benzodiazepines (anxiolytics)	*Clorazepate					■			
	Lorazepam	✔		N05BA06	✔	■		☑	☑
	Oxazepam	✔				■	■	☑	☑
	Clonazepam	✔		N03AE01	✔	■	■	☑	☑
	Diazepam	✔		N05BA01	✔	■	■	☑	☑
	Chlordiazepoxide	✔		N05BA02	✔	■	■	☑	☑
	Bromazepam	✔		N05BA08	✔	■	■	☑	☑
	Clobazam	✔		N05BA09	✔	■	■	☑	☑
	Prazepam	✔		N05BA11	✔	■	■	☑	☑
	Alprazolam	✔		N05BA12	✔	■	■	☑	☑
Benzodiazepines (sedatives)	Flurazepam	✔		N05CD01	✔	■	■	☑	☑
	Nitrazepam	✔		N05CD02	✔	■	■	☑	☑
	**Flunitrazepam		✔	N05CD03		■	■	☑	☑
	Triazolam	✔		N05CD05	✔	■	■	☑	☑
	***Lormetazepam	✔		N05CD06	✔	■	■	☑	
	Temazepam		✔	N05CD07	✔	■	■	☑	☑
	Midazolam	✔		N05CD08	✔	■	■	☑	☑
Benzodiazepines (NPS)	Estazolam	✔				■	■	☑	
	Adinazolam					(■)	(■)	☑	▯
	Diclazepam					(■)	(■)		▯
	Etizolam					(■)	(■)	☑	☑
	Flualprazolam					(■)	(■)	☑	☑
	Flubromazepam					(■)	(■)	☑	
	Flubromazolam					(■)	(■)	☑	▯
	Flunitrazolam					(■)	(■)		▯
	Phenazepam	✔				(■)	(■)	☑	☑
Z-drugs	Zopiclone	✔		N05CF01	✔			☑	☑
	Zolpidem	✔		N05CF02	✔			☑	☑
	****Zaleplon	✔		N05CF03				☑	☑
Gabapentinoids	Gabapentin			N03A×12	✔			▯	☑
	Pregabalin			N03A×16	✔			▯	☑
Opioid agonist treatment	Buprenorphine		✔	N07BC01 N07BC51			■		☑
	Methadone		✔	N07BC02		■	■	☑	☑
Prescription opioids	Fentanyl		✔	N01AH01 N02AB03	✔		■	▯	☑
			✔	N01AH51					
	Alfentanil		✔	N01AH02			■		
	Morphine		✔	N02AA01	✔	■	■	☑	☑
			✔	N02AG01 N02AA51					
	Oxycodone		✔	N02AA05 N02AA55	✔		■	▯	☑
			✔	N02AJ18 N02AJ17 N02AJ19					

Continued

Table 1 Continued

Group	Substance	Controlled under the Misuse of Drugs Act 2017		Prescription/Dispensing records		Class specific testing (immunoassay)		Analyte specific testing (LCMS)	
		Schedule 4	Schedule 2 or 3	ATC codes	GMS/Prisons	NDTC	MBRS 2010–2018	MBRS 2019–2020	State Laboratory
	Dihydrocodeine		✔	N02AA08	✔	■	■	▯	☑
			✔	N02AJ03 N02AJ02 N02AJ01 N02AA58					
	Pentazocine		✔	N02AD01			■		
	Buprenorphine		✔	N02AE01	✔		■		☑
	Nalbuphine		✔	N02AF02			■		
	Pethidine		✔	N02AB02 N02AG03 N02AB72 N02AB52			■	▯	☑
	Hydromorphone		✔	N02AG04		■	■		
			✔	N02AA03	✔				
	Tramadol			N02A×02	✔		■	▯	☑
				N02AJ14 N02AJ13	✔				
				N02AJ15					
	Meptazinol			N02A×05	✔		■		
	Tapentadol		✔	N02A×06	✔		■		☑
	Codeine		✔	N02AA59 N02BE51 N02AJ07 N02AJ06	✔	■	■	☑	☑
			✔	N02AJ09 N02AJ08 N02AA79					
Cough suppressants	Hydrocodone		✔	R05DA03		■	■	▯	
	Codeine		✔	R05DA04	✔	■	■	☑	☑
Psychostimulants	Dexamfetamine		✔	N06BA02					
	Methylphenidate		✔	N06BA04	✔			▯	▯
	Modafinil			N06BA07	✔				
	Atomoxetine			N06BA09	✔				
	Lisdexamfetamine		✔	N06BA12	✔				
	Solriamfetol			N06BA14					
	Idebenone			N06B×13	✔				

Authorisation withdrawn in *2005, **2013, ***2020 and ****2015.
■ Immunoassay: only identifies the drug class of the drugs detected.
(■) Immunoassay: probable reactivity.
▯ LCMS: analyte specific screening testing scope.
☑ LCMS: analyte specific screening and confirmatory testing scope.
ATC, Anatomical Therapeutic Chemical; GMS, General Medical Scheme; LCMS, Liquid chromatography mass spectrometry ; MBRS, Medical Bureau of Road Safety; NDTC, National Drug Treatment Centre; NPS, New psychoactive substances.

Presentations of intentional drug overdose involving other agents such as chemicals (ICD-10X66-69) and alcohol-only self-poisoning cases (ICD-10X65) will be excluded. Drugs taken are captured via self-report, ambulance service records, hospital medical records and toxicology reports. Information relating to a maximum of 10 drugs taken in intentional non-fatal overdose cases are recorded. Information on the source of the drugs taken is not recorded. Anonymised individual level data, including age and gender, will be used to evaluate trends in non-fatal intentional drug overdose presentations involving PDPM, both alone and in combination with other substances.

The NDTRS is the national epidemiological surveillance database that records and reports on treated problem drug and alcohol use in Ireland.[19] It complies with the EMCDDA data collection protocol for their Treatment Demand Indicator, allowing for comparison with other treatment data in Europe. Treatment data are provided by statutory and non-statutory services,

Table 2 Summary of the data sources and outcomes examined across the three inter-related studies

Source	Main outcomes
Study 1	
Forensic Science Ireland (FSI)	Number of drug seizures involving PDPM (by drug class, individual drugs) per annum
Health Products Regulatory Authority (HPRA)	Number of drug detentions involving PDPM (by drug class, individual drugs) per annum
Health Service Executive (HSE)—General Medical Scheme (GMS)	Monthly prevalence rate of PDPM (drug class, individual drugs) per 10 000 GMS eligible population aged >16 years; total quantity dispensed ► Overall, and by gender, age-group and geographical area
Irish Prison Services (IPS)	Monthly prevalence rate of PDPM (drug class, individual drugs) per 10 000 prison population aged >18 years; total quantity dispensed ► Overall, and by gender and age-group
Study 2	
National Drug and Alcohol Survey (NDAS)	Annual weighted prevalence rate of (self-reported) past-year sedative, tranquiliser and opioid use ► Overall, and by gender, age group, geographical location and education level
Medical Bureau of Road Safety (MBRS)	Annual detection rates for PDPM (drug class between 2010 and 2018; individual drugs 2019 and 2020) per 1000 drug tests, and per 10 000 licenced drivers ► Overall, by gender and age group
State Laboratory	Annual detection rates for PDPM (drug class, individual drugs) per 1000 postmortem cases
National Drug Treatment Centre Laboratory (NDTC)	Annual rate of people testing positive at least once for PDPM per 1000 people tested ► Overall and by age group
Study 3	
National Drug Treatment Reporting System (NDTRS)	Annual prevalence rates of treatment demand for PDPM (alone and in combination with other drugs) per 10 000 population, and per 1000 seeking treatment for problem drug use ► Overall, by gender and age group
National Drug Related Death Index (NDRDI)	Annual standardised drug-poisoning death rates per 10 000 population ► Overall, by gender and age group
National Self-Harm Registry Ireland (NSHRI)	Annual rates of intentional non-fatal overdose presentations involving PDPM (alone and in combination with other drugs and/or alcohol per 10 000 population, per 1000 self-harm presentations, and per 1000 intentional drug overdose presentations) ► Overall, by gender and age group

PDPM, prescription drugs with potential for misuse.

including outpatient services, residential centres, prisons and general practitioners. The primary drug problem and up to four additional problem drugs are recorded for each case. Anonymised case level data, including age and gender, will be used to evaluate trends in treatment demand for problem drug use involving PDPM.

Outcomes indicators

Table 2 provides an overview of the outcomes assessed across the three studies. Study 1 will involve describing trends in the drug supply market of illicit PDPM using law enforcement drug seizure and detention data. Consistent with the EMCDDA, we will report on the number of drug seizures, allowing for comparison with other European countries.[18] Number of seizures represents the best indicator of trends for the illicit supply of drugs, as quantities seized is vulnerable to variation from large individual seizures.[20] This study will also include two repeated cross-sectional studies of prescribed medications dispensed to people (1) eligible for the GMS in the community and (2) in prison during the observation period. Monthly prevalence rates for PDPM (individual drugs) per 10 000 GMS eligible population and per 10 000 prison population (drug class and individual drugs) will be presented with 95% CIs. Median and IQRs of monthly prevalence rates and quantity dispensed will be reported overall, and by gender and age group.

Study 2 will report on patterns of use of PDPM, using anonymised individual level data from the three national drug and alcohol surveys. The weighted prevalence of past-year sedative and tranquiliser use, and opioid use (excluding heroin) will be calculated for each survey year, with 95% CIs. Estimates of self-reported use will be reported by age, gender and geographical locations. Sampling weights will be used in all analyses. These weights adjust estimates for excluded populations and survey nonresponse.[21]

Annual detection rates for PDPM in MBRS data will be calculated as the number of positive screenings per 1000

tests, and per 10 000 licenced drivers. Similarly, annual detection rates postmortem will be calculated per 1000 postmortem cases (by drug class, and where possible by individual drug). Detection rates among people attending the NDTC will be calculated as the number of people with at least one positive screening (by drug class) per 1000 adults attending the NDTC.

Study 3 will provide detail on the health burden associated with the use of PDPM. Using anonymised individual level data from the NDRDI, annual standardised drug-poisoning death rates involving PDPM will be calculated per 10 000 population. Standardised mortality rates for each year of the study period will be calculated per 10 000 population, standardised to the European Standard Population. Anonymised data from the National Self-Harm Registry will be used to calculate annual rates of intentional non-fatal overdose presentations involving PDPM (alone and in combination with other drugs and/or alcohol) per 10 000 population, per 1000 self-harm presentations, and per 1000 intentional drug overdose presentations between 2010 and 2020. Finally, using anonymised records from the NDTRS, we will calculate annual prevalence rates of treatment demand for problem drug use involving PDPM (alone and in combination with other problem drugs) per 10 000 population, and per total number of cases seeking treatment from 2010 to 2020.

Statistical analysis plan

Statistical analysis will involve examining trends in rates (or standardised rates) over time, and will use negative binomial regression models, reporting incidence or prevalence rate ratios with 95% CIs. Where available, independent variables age, gender, region (county) and other relevant factors will be included in the regression models. If our analyses of crude trends suggest inflexion points at certain time points, we will model year as categorical (for non-linear association) or, if appropriate, use joinpoint regression and present annual percentage changes and average annual percentage changes.[22] Associations between rates (overall, and by specific drug group) of supply, use and health burden, will be explored visually, and where appropriate using correlation analyses. Stata (V.16.0) and SAS Enterprise Guide (v) will be used for all analyses and significance at $p<0.05$ assumed.

Public and patient involvement

The research question and outcome measures were developed in collaboration with the study public and patient involvement coauthor (MOV). MOV is the Community Development Officer at UISCE, the National Advocacy Service for People who use Drugs (PWUD) in Ireland. UISCE is currently the advocate/representative for the community of PWUD at the National Drug Strategy Steering Group. The PI (GC) liaised with UISCE on multiple occasions regarding the appropriateness and relevance of the research topic, the study design and the dissemination plan. UISCE will be part of the project steering group and will be involved at group meetings to ensure representation of patients' views and to provide input into study design, planning, conduct, analysis, interpretation and dissemination to ensure a patient-centred approach.

Ethics and dissemination

The study has received approval from the RCSI Ethics Committee on 4 April 2022 (REC202202020). The programme of research has been planned to ensure compliance with the European General Data Protection Regulation (GDPR) 2018, the Data Protection Act 2018, and the Data Protection Act 2018 (Section 36(2)) (Health Research) Regulations 2018. As the data used in this project will be anonymised, and mostly aggregated, they are outside the remit of the General Data Protection Regulations. Despite the very limited potential risk for re-identification of the data, good data practices and data security arrangements will be applied to all data involved in this study. This will include clear and transparent data usage agreements with the data providers. In addition, we will publish data in tabular, aggregate forms only, and cells containing data from less than five individuals will be suppressed. We will not disclose individual results. A data risk assessment has been completed for this project in accordance with the Data Protection Act. Data security and management will involve processes to ensure data quality, and storing data on a password protected and encrypted device, which will only be accessible by researchers with permission to access and analyse the data. We will report our findings in accordance with the Reporting of studies Conducted using Observational Routinely collected health Data statement. We will disseminate project findings at scientific conferences and in peer-reviewed journals. We will aim to present findings to key stakeholders via research briefs and presentations, to maximise translational impact of research findings.

DISCUSSION

The European Commission has underlined the importance of being better prepared for future drug trends, to inform proactive drug policy and strengthen national monitoring and intervention capacity. However, there is a paucity of evidence in relation to the misuse of prescription medicines, particularly psychoactive substances, in the EU. Furthermore, evidence from North America may not translate to EU countries due to differences across healthcare systems, regulatory frameworks and prescribing practices.[23] Identifying relevant and accessible means of surveillance in EU countries, allowing for the detection of drug trends, is an essential first step in this process. This is the first study to use multiple early warning systems, drug supply and epidemiological indicators to examine trends in the use and harms associated with PDPM in Ireland. In addition, this study will identify the current strengths and weakness of the included data sources, as a means of monitoring drug trends in Ireland. Access to demographic details, such

as age and gender (where available), will allow us to effectively monitor trends across groups.[24]

It is important to stress that prescribing opioids, benzodiazepines, gabapentinoids or psychostimulants should not be restricted if a patient with a legitimate need can benefit, however appropriate and safe prescribing is vital if the health and well-being of the population is to be safeguarded. This research could have a clear role in informing health services, shaping national policy around the prescribing of certain drugs, or combinations of drugs, and as a direct consequence, enhancing population health. However, a number of shortcomings should be considered. First, prescribing trends in the community will rely on dispensing records from the GMS database, which represents approximately one-third of the Irish population, and is over-representative of people with a lower socioeconomic status, women and older age.[16] Second, analysis of forensic toxicology data to estimate trends in the detection rates of PDPM over time, will be influenced by the screening methodology used. For example, use of immunoassay will only allow for the detection of a drug class (eg, benzodiazepines) rather than individual drugs within the drug class (eg, diazepam). In contrast LC-MS-MS, will allow for the detection of specific drugs, including New Psychoactive Substances, if the laboratory had the relevant reference standard to detect that specific drug. Third, all analyses will rely on anonymised data, to ensure compliance with GDPR, therefore data linkage across datasets is not possible. Therefore, any examination of relationships between aggregate population trends will be limited to ecological analyses. Any associations will serve as hypothesis generating. Notwithstanding these limitations, findings from this study will inform Ireland's drug monitoring system and support evidence informed practice and service provision. This work has the potential to contribute to the WHO Sustainable Development Goal 3, specifically the goal of reducing premature mortality including suicide, and strengthening the prevention and treatment of substance abuse.

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