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2020

BJA
British Journal of Anaesthesia

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Journal:	*British Journal of Anaesthesia*
Manuscript ID	BJA-2020-00250-HH149.R1
Article Type:	Clinical Investigation
Date Submitted by the Author:	n/a
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Keywords:	gabapentinoids, data linkage, prescribing, mortality, drug related deaths, co-prescribing

Trends in gabapentinoid prescribing, co-prescribing of opioids and benzodiazepines, and associated deaths in Scotland

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Abstract

Background: Gabapentinoid drugs (gabapentin and pregabalin) are effective in neuropathic pain, which has a prevalence ~7%. Concerns about increasing prescribing have implications for patient safety, misuse and diversion. Drug-related deaths (DRDs) have increased and toxicology often implicates gabapentinoids. We studied national and regional prescribing rates (2006-2016) and identified associated sociodemographic factors, co-prescriptions and mortality, including DRDs.

Methods: National data from Information Service Division, NHS Scotland. Prescribing, sociodemographic and mortality data from Health Informatics Centre, University of Dundee. DRDs where gabapentinoids were implicated identified from National Records of Scotland and Tayside Drug Death Databases.

Results: From 2006-2016, the number of gabapentin prescriptions in Scotland rose 4-fold (164,630 to 694,293), and pregabalin 16-fold (27,094 to 435,490). In 2016 'recurrent users' (≥3 prescriptions): mean age 58.1years, mostly females (62.5%) and more likely to live in deprived areas. 60% were co-prescribed an opioid and/or benzodiazepine (opioid 49.9%, benzodiazepine 26.8%, both 17.1%). Age-standardised death rate in those prescribed gabapentinoids was double the Scottish population (RR 2.16, 95% CI 2.08-2.25). Increases in gabapentinoids contributing to cause of DRDs were reported regionally and nationally (gabapentin 23% vs 15%; pregabalin 21% vs 7%). In Tayside, gabapentinoids were implicated in 22 (39%) DRDs, 17 (77%) of whom had not received a prescription.

Conclusions: Gabapentinoid prescribing has increased dramatically since 2006, as have dangerous co-prescribing and death (including DRDs). Older people, women and those living in deprived areas were particularly likely to receive prescriptions. Their contribution to DRDs may be more related to illegal use, with diversion of prescribed medication.

Keywords: data linkage, drug related deaths, gabapentinoids, mortality, prescribing

Introduction

Initially developed to treat epilepsy, gabapentinoid drugs (gabapentin and pregabalin) are also widely used in the UK for the treatment of neuropathic pain, (for which they are licenced) migraine and generalized anxiety disorder in adults (pregabalin only).[1]

Chronic pain is common: 19% of the population in Europe were found to have chronic pain[2] and 7-10% of the population have pain with neuropathic features.[3] Neuropathic pain is more severe and difficult to treat than non-neuropathic pain, resulting in serious detrimental impact on quality of life.[4,5] Gabapentinoids have been shown to be effective in treating neuropathic pain and are indicated as first-line treatments in national and international clinical guidelines.[6-8]

There have been significant increases in the number of prescriptions for gabapentinoids in the past decade in Scotland and the UK,[9-11] as well as in North America [12-14], and Europe.[15 16] rief reports have found the rate of patients newly treated with gabapentinoids has increased 3-4 fold since 2002 [9 12] and similar increases in the number of 'gabapentinoid-involved' visits to a doctor have recently been reported.[17] These increases cannot necessarily or wholly be explained by the number of cases of neuropathic pain or other relevant conditions. It has been suggested that clinicians, seeking alternatives to the prescribing of opioids[18] and concerns about long term NSAID and coxib prescribing,[19] are responding by lowering the threshold for prescribing gabapentinoids for various types of pain, with prescribing still increasing in England, despite reclassification as a Class C drug.[20]

There have been concerns about possible misuse of gabapentinoids, often along with opioids, resulting in diversion and dependence issues.[21,22] The co-prescribing of gabapentinoids, opioids and benzodiazepines is particularly concerning[9] and is not unusual in patients with severe chronic pain, potentially putting them at high risk of overdose and dependency.[23]

Drug-related deaths are of particular public health concern currently. Prescribed gabapentinoids have been associated with increased risk of suicidal behaviour, as well as unintentional overdose, injuries, road traffic accidents and violent crime.[24] In Scotland, drug-related deaths have doubled in the past ten years, resulting in the highest rate recorded in the EU in 2018.[25] Gabapentin was implicated in 15.2% of these drug-related deaths and pregabalin in 16.5%. This is a substantial increase compared to only 3% and <1% in 2012 respectively.[25] Drug-use disorders are also a major contributor to health inequalities as they are the greatest of cause of years lost due to ill health, disability or early death in the most deprived areas.[26] In April 2019, gabapentin and pregabalin were reclassified as class C controlled substances in the UK, with greater restrictions on their prescribing due to concerns about their misuse and the growing number of deaths associated with the misuse of these drugs.[27 28] Scotland is recognised as having one of the most developed recording mechanisms for drug-related deaths worldwide including details from death registrations, supplemented by toxicology information and the use of well-defined criteria.[25]

In this study, we describe national and regional prescribing rates of gabapentin and pregabalin over an eleven-year period (2007 to 2016) and identify associated socio-demographic factors and co-prescribing. Data from well-defined, robust datasets are examined to determine factors associated with co-prescribing and with drug-related deaths information.

Methods

Data sources

National prescribing data

The National Health Service (NHS) in Scotland is administered through 14 geographical NHS Boards. The Prescribing Information System (PIS) is a national individual-level dataset of prescriptions issued, dispensed and reimbursed within community pharmacies[29] and all prescribing data are stored securely by the Information Services Division (ISD), part of NHS Scotland (http://www.isdscotland.org/). General Practitioners (GPs) account for more than 95% of community prescribing and capture from prescriptions is high at 98.7% for GP prescribers.[29]

We examined national level data from ISD. Prescribing data for two NHS Health Board regions in Scotland (NHS Tayside and NHS Fife) were provided by the Health Informatics Centre (HIC), University of Dundee (https://www.dundee.ac.uk/hic). HIC was established over 10 years ago, is recognised as a leader in health data linkage and maintains a clinical data repository of eHealth data, including prescribing. HIC combines routine collected datasets for the Tayside and Fife population covering approximately 20% of the Scottish population.

Utilising both data sources, we examined:

1. the trend in number of prescription items of gabapentin and pregabalin (2006-2016) http://www.isdscotland.org/ (data from NHS Fife available from 2010)
2. factors associated with receiving a gabapentinoid prescription including socio-demographic factors, co-prescribing and mortality.
3. drug-related deaths data, including those associated with gabapentin or pregabalin, obtained from National Records of Scotland (NRS) (2007-2016) https://www.nrscotland.gov.uk/statistics-and-data/statistics/statistics-by-theme/vital-events/deaths/drug-related-deaths-in-scotland. The Office for National Statistics (ONS) 'wide' definition was used which includes all deaths coded to accidental poisoning, and to intentional self-poisoning by drugs, medicaments and biological substances, whether or not

a drug listed under the Misuse of Drugs Act was present in the body.[30] The use of the 'wide' definition enabled us to examine the toxicology reporting of gabapentin and pregabalin separately.

Individual prescribing data from NHS Tayside & Fife

HIC conducted a prescribing linkage of all individuals who were dispensed at least one prescription for gabapentin or pregabalin in 2016 in NHS Tayside and NHS Fife in Scotland (combined population approx. 780K). This eHealth record linkage used a unique person identifier, the Community Health Index (CHI) number. Data were linked between the following datasets: prescription medicines dispensed by community pharmacies; demography data (age, gender, Scottish Index of Multiple Deprivation (SIMD), urban/rural categorisation of residence) and death records from General Records Office of Scotland (GROS). SIMD is based on residential postcode and grouped into quintiles, ranking those areas from most deprived (ranked 1) to least deprived (ranked 5). All data were pseudo-anonymised and stored in the HIC Safe Haven for analysis.

Prescribing data

Gabapentinoid drugs, gabapentin and pregabalin, detailed in Chapter 4.8.1 of the British National Formulary (BNF)[1] were included. The BNF is a UK pharmaceutical reference source that contains guidance on prescribing, dispensing, administering and pharmacology about medicines available in the UK. To examine co-prescribing, we also included all opioid drugs (BNF Ch 4.7.2) and benzodiazepines (BNF Ch 4.1.1/4.1.2). "Recurrent users" of gabapentinoids were defined as those who received three or more prescriptions in the one year period, to exclude those patients who were prescribed a short trial of these drugs.

Deaths

The age standardised mortality for patients prescribed a gabapentinoid in NHS Tayside and Fife in 2016 was compared with Scottish national age standardised mortality data.[31] The underlying cause of death was divided into three groups (circulatory deaths, respiratory deaths and all-cause mortality) to conform to the NRS categories. The standard population used to calculate age-standardised death rates was the 2013 European Standard Population (ESP). The ESP is a theoretical population defined as having a particular distribution by age, which enables comparisons between different countries or populations.[31]

Drug-related deaths (DRDs) are identified using details from death registrations supplemented by toxicology information obtained from forensic pathologists and are defined as deaths (intentional or unintentional) due to the effect of opioids, cannabinoids, sedatives or hypnotics, cocaine (or other stimulants), hallucinogens or other psychoactive substances.[25] Deaths that have occurred due to a complication of the immediate or short-term use of drugs listed above e.g. bronchopneumonia due to heroin intoxication, are also considered drug-related deaths. GROS data included details of the underlying cause of death, classified according to ICD-10 codes. Drug-related deaths are identified by the NRS using ICD-10 codes (see above). NRS also reports drug-related deaths using the ONS definition, which is wider and includes deaths coded to volatile substances and deaths not restricted to cases where a drug listed under the Misuse of Drugs Act (1971) was known to be present at the time of death.[30] Given that the NRS report only presents gabapentin and pregabalin specific data for the ONS 'wide' definition, this definition has been used for the reporting of the national statistics in this paper.

Data from Tayside were obtained from the Tayside Drug Death Database, which informs the work of the Tayside Drug Death Review Group (TDDRG).[32] Suspected drug deaths are notified to the Health Intelligence team within NHS Tayside Public Health by the Tayside Division of Police Scotland. Additional information is then collected from partner agencies, assimilated and subsequently reviewed alongside the post-mortem and toxicology findings by the TDDRG. As part of the

comprehensive case review, the TDDRG determines if a case should be considered a drug death or not. Drug deaths are defined by this Group as the presumed non-intentional fatal overdoses of illicit (or illicitly obtained controlled) substances and therefore represent a subset of drug-related deaths.

Ethical approval

Anonymised record linkage was conducted according to Health Informatics Centre (HIC), University of Dundee, Standard Operating Procedure (SOP) (https://www.dundee.ac.uk/hic). The Tayside Research Ethics Committee does not require submission of individual studies that follow this SOP which is Caldicott Guardian approved.

Statistical analysis

Mainly descriptive analyses were conducted to examine eleven-year trends (2006-2016) in community prescribing of gabapentinoid drugs across Scotland, NHS Tayside and NHS Fife; the sociodemographic characteristics of those receiving prescriptions; recurrent users of gabapentinoids, and prescribing of gabapentinoids along with opioids and/or benzodiazepines in 2016. Continuous variables are presented as mean ± SD and were analysed by independent t-test for difference in mean between groups. Categorical variables are presented as counts (percentages). The associations of age, gender and SIMD with recurrent users of gabapentinoids in 2016, and with co-prescribing were examined using multivariate logistic regression and we calculated odds ratios (ORs) and 95% confidence intervals (CIs) for both comparisons. Relative risk and 95% CIs were calculated for each age standardised mortality rate. We used a threshold of 5% ($p<0.05$) for statistical significance in our analyses. All statistical analyses were conducted using IBM SPSS Statistics v 22, R 3.1.1 [https://www.r-project.org/] and OpenEpi, version 3.01 [https://www.openepi.com/Menu/OE_Menu.htm].

Results

The number of gabapentin prescriptions in Scotland rose four-fold from 164,630 in 2006 to 694,293 in 2016, with greater rises in the number of pregabalin prescriptions (Figure 1). In NHS Tayside gabapentin prescriptions numbered 16,481 in 2006 to 57,472 in 2016 (x3.5) and in NHS Fife, there were 20,465 prescriptions issued in 2010, rising to 65,241 in 2016 (x3.2). Comparative rates in prescribing are shown in Figure 1.

Sociodemographic characteristics

In NHS Tayside and NHS Fife, 29,111 patients were prescribed a gabapentinoid in 2016, representing 3.7% of the population of the two NHS Board areas. Of these, almost three quarters (73.2%, n=21,335) were recurrent users with 3 or more dispensed prescriptions (Table 1). The mean age of recurrent users was 58.1 years (SD 15.6), the highest proportion were women (62.5%) and they were more likely to live in areas of highest deprivation (SIMD quintile 5). The largest proportion of the recurrent users lived in urban areas (70.5%).

Co-prescribing of opioids and/or benzodiazepines

Co-prescribing was common, with almost 60% of those receiving gabapentinoids also prescribed an opioid and/or a benzodiazepine in 2016 (Table 2). Similar rates of co-prescribing of opioids were seen among both males and females (50%) although there was significantly higher co-prescribing of benzodiazepines in females (28.5% vs 24.2%, $p<0.05$). The socio-demographic characteristics are shown in Tables 3 and 4. The mean age of the patients prescribed gabapentinoids along with opioids and/or benzodiazepines was 57.3 years (SD 15.8). Most of them were in the 41-60 years age group ($p<0.01$) and there was a higher proportion of women compared to men (63.6% vs. 36.4 %, $p<0.0001$). The majority of those receiving such a co-prescription resided in an urban area (70%, $p=0.006$), and they were more likely to live in the most deprived areas ($p<0.001$).

Recurrent prescriptions of gabapentinoids were significantly associated with older age (age 41-60 years, OR 1.08 (95% CI 1.06 – 1.10) and living in more deprived areas (compared to SIMD 1 most deprived, SIMD 3, OR 0.94 (95%CI 0.92 – 0.95)) (Supplementary Table 2).

Deaths

In total, there were 1,312 deaths in 2016 identified in the dataset (4.5% of those prescribed a gabapentinoid in 2016), with 54 of these (4.1%) classified as 'drug-related deaths'. Compared with the Scottish general population the age standardised all-cause mortality was significantly higher in individuals prescribed gabapentinoids in NHS Tayside and Fife 2016: RR 2.16 (95% CI 2.08- 2.25, p<0.001) and for deaths due to respiratory disease (RR 1.32, 95% CI 1.15-1.50, p<0.001), although not for deaths due to circulatory disease (RR 1.03, 95% CI 0.91-1.41, p=0.64). (Supplementary Table 3)

Drug-related deaths

There has been a steady increase in the number of drug-related deaths in Scotland and in NHS Tayside where gabapentin and pregabalin were implicated in or potentially contributed to the cause of death. (Figures 2a & 2b), although the percentages are higher in Tayside compared to the national rates for both drugs (gabapentin 23% vs 14%; pregabalin 33% vs 12% in 2017).

In Tayside, gabapentin or pregabalin were implicated in the cause of death (as stated in post-mortem cause of death) in 22 of 56 (39%) drug deaths in 2016. In 17 (77%) of these fatalities, the person had not been prescribed a gabapentinoid. In 2016, gabapentinoids were the third most common group of substances to be found in toxicology of drug deaths at post-mortem (39 detections of pregabalin and/or gabapentin), after opioids and benzodiazepines."

People in whom a gabapentinoid was identified as contributing to the cause of drug death in Tayside in 2016 were slightly younger (mean age 37.2 years vs 40.2 years), more frequently male (82% vs 76%), and a higher proportion were more likely to be living in areas of greater socioeconomic deprivation, although these differences were not statistically significant (Supplementary Table 4).

Discussion

This study confirms the rapidly rising rate of gabapentinoid prescribing in Tayside and Fife, mirrored across Scotland. We found high rates of potentially dangerous co-prescribing of drugs that can interact with gabapentinoids, with 60% co-prescribed an opioid and/or a benzodiazepine (50% were co-prescribed an opioid and 27% a benzodiazepine only). Factors associated with gabapentinoids prescribing and co-prescribing include older age, female gender and deprivation. Overall rates of DRDs in Scotland have increased,[25] and DRDs where gabapentinoids are implicated or potentially contributed, has also increased as a proportion of all DRDs. This 'contribution' is found in approximately 26% of DRDs nationally and 47% in Tayside. This increase is at a similar rate to the increases in overall prescribing rates, implying that these may be connected.

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The completeness rate of the prescribing data, and community pharmacy dispensed prescriptions of gabapentinoids across Scotland (including NHS Tayside & Fife), is high.[29] This produced a large and comprehensive study population, minimising selection bias and enabling analysis of some individual level socio-demographic characteristics. This is an advantage compared to studies that are restricted by prescription data from health insurance plans and claims data.[33] However, data on individual characteristics were limited, which was necessary to maintain anonymity and minimise risk of potential disclosure of individual patients, resulting in mainly descriptive analysis and restricting the possibility of more complex statistical analyses. Furthermore, the prescribing data lacked clinical details and we were unable to associate gabapentinoid prescriptions with specific diagnoses including neuropathic pain or epilepsy. Also, although we were able to determine those patients who received a prescription for gabapentinoids and/or opioids and benzodiazepines in the same year, we are unable to confirm prescribing at the same time in the year.

Rising rates of gabapentinoids prescribing have been reported internationally.[9-16, 34 35] Although these rates are generally comparable with our findings, these other studies report on different objectives,

including a focus on treatment of neuropathic pain[10,16], for epilepsy and non-epilepsy disorders [14-16], restricted to only pregabalin prescribing[13,16] and limited by data from a panel survey[12] or public insurance data.[13]

This paper focuses on all primary care gabapentinoids prescribing with detailed analysis of trends and associated socio-demographic characteristics and mortality with individual level data. The context of gabapentinoids use in Scotland is particularly important and distinctive given the highest rate of DRDs in Europe and the availability of detailed information from toxicology reports, contributing to a more complete picture of use and potential misuse.

In England, 3.3% of the population were prescribed gabapentinoids in one year (2017-2018) and 12.8% were prescribed opioids.[35] We found similar rates of gabapentinoid prescribing in Tayside (3.7%) and other research reported opioid analgesic prescribing rates at 11% in Tayside and a higher rate of 18% of the population in Scotland.[11,37] The socio-demographic characteristics associated with gabapentinoid prescribing included age, with highest rates of prescribing found in 40-60 year olds, female gender and deprivation. Similar findings have also been reported for patients in England [35] and these sociodemographic characteristics are also associated with reporting of chronic and neuropathic pain, and with opioid prescribing.[37,38] Because gabapentin and opioids are both commonly prescribed for chronic pain, the likelihood of co-prescription is high.[21,39] Other research has found 20% of all patients prescribed either gabapentin or pregabalin are also taking an opioid [9], whereas our data find a higher rate of co-prescribing of opioids at 50% of patients, and with 27% co-prescribed a benzodiazepine. This is concerning as, on their own, prescribed gabapentinoids have been associated with an increased risk of suicidal behaviour, unintentional overdoses, head/body injuries, road traffic incidents and offences,[24] and in combination with other medications, such as opioids or benzodiazepines, further increases in the risk of serious side-effects and overdose.[9 37 39]

Although initially presumed to have no abuse potential, a systematic review estimated the prevalence of gabapentin misuse in the general population to be 1%, 40–65% among individuals with prescriptions, and between 15% and 22% within populations of people who abuse opioids.[21] Gabapentinoids are misused primarily for recreational purposes, self-medication or intentional self-harm and are misused alone or in combination with other substances, especially opioids, benzodiazepines and/or alcohol.[22,24, 39,40]

In a nested case-control study of opioid users, 8% of patients receiving opioids were co-prescribed gabapentin, and co-prescription was associated with a 50% increase in opioid-related death.[40] In Scotland in 2010, gabapentin and/or pregabalin were implicated in, or potentially contributed to the cause of death in approximately 1% of all DRDs[22] compared to data from 2018 [25] where this figure rose to 13.7% of all DRDs. In Tayside this figure is even higher at 23% (although this may in part be due to differences in drug death definitions). DRDs include deaths that have occurred due to acute complications e.g. bronchopneumonia, however patients on prescribed opioids may not be identified as such, leading to the possibility of under-reporting. Aside from gender, where males are at higher risk, DRDs follow a similar sociodemographic pattern to gabapentin and opioids prescribing.[37,38] Prescribing rates were higher in females but DRDs, where gabapentinoids are implicated, were higher in males in Tayside, suggesting that drug diversion may be an issue. Overall, these findings support claims that prescribing is related to serious harms and/or have similar underlying causal factors.

Drug-use disorders are the number one contributor to burden of disease in the most deprived areas of Scotland.[26] Problematic drug use and DRDs are strongly associated with health inequality, as is gabapentinoid prescribing, and the prevalence of neuropathic pain.[38] The average age of a person dying unintentionally as a result of illicit or illicitly acquired drug use in Tayside is currently 40.2 years. This compares to the national average age of death in Scotland of 81 years for females and 77

years for males [41] and represents a gross health inequality in our population. The majority of drug deaths occur in people who have experienced considerable life adversity, often from a young age. Factors that influence risk are multi-dimensional, and problematic drug use is rarely an independent choice by an individual but the result of a complex interplay of social, economic and health factors.[42] The Public Health Minister for Scotland has said "What Scotland faces in terms of drug deaths is an emergency" and has consequently established a task force to promote action with the aim of improving health outcomes for people with problematic drug use.[43]

Whilst understanding the development of problematic drug use is more complicated than studying the specific substances involved, affordability and availability will impact on which substances are accessed by individuals. Currently, emerging trends show increases in the involvement of three key substance groups in drug-related deaths: atypical diazepams (principally etizolam), gabapentinoids and cocaine.[25] Each have different supply and distribution routes. Etizolam can be manufactured domestically and cocaine imported and both are illicit substances. In contrast, gabapentinoids are prescribed medication and diversion of gabapentinoids appears to be an important risk factor in DRDs in Tayside, where toxicology reported the presence of these substances but further investigations found that they had not been prescribed to the vast majority of casualties.[32] Other studies have confirmed toxicology reports without prescription or medical indication indicating that diversion is not uncommon.[21,44] How the diversion of gabapentinoids occurs is uncertain and warrants further investigation.

Conclusions

Prescribing of gabapentinoids has increased dramatically since 2006, as have the associated potential harms, dangerous co-prescribing and death (including DRDs). This study has important implications for preventive measures, aiming to reduce serious harms in the population. The public health emergency that has arisen from the increasing number of DRDs might be partly addressed by

attention to gabapentinoid prescribing, but is also likely to require wider public health and political approaches to the common factors underlying the aetiology of chronic pain, substance misuse and DRDs.[45]

Authors contributions

Project conception and design for the prescribing data linkage: N.T., B.H.S, L.A.C, H.L.H, P.T.D.
Statistical analysis of the HIC data and age-standardised death rates: A.V., Y.Z., P.T.D., J.W. Statistical analysis of the national and Tayside DRDs data: E.F., E.M.
Submission draft: N.T.
Critical revisions of the work for important intellectual content: all authors
Final approval of the manuscript to be published: all authors

Declaration of interests: BHS is National Lead Clinician for Chronic Pain in Scotland. BHS and LAC, and are members of the National Advisory Committee for Chronic Pain (Scotland) and have contributed to the National Quality Prescribing Strategy (including gabapentinoids). They contributed to the SIGN Guideline 136 (Management of Chronic Pain) update on opioid use in chronic pain, 2019. LAC is a member of the MHRA Expert Working Group on Opioids. PTD reports grant funding from Shire, Gilead and AbbVie, outside the submitted work. PTD is a member of the New Drugs Committee of the Scottish Medicines Consortium. EF is the Chair of the Tayside Drug Deaths Review Group, which as per the annual report cited in the paper, seeks to make strategic recommendations for partner agencies and organisations to implement to reduce risk of future drug deaths. EM is the drugs death analyst for NHS Tayside. The regional Tayside data used in the paper is from the annual reports informed by the database which she maintains. NT, AV, HLH, JW and ZY have no declarations to report.

Funding: Tenovus Scotland, Tayside (T16/34).

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Table 1. Characteristics of patients in NHS Tayside & Fife Health Board areas prescribed gabapentinoids in 2016

	Gabapentinoids users (n=29,111)	**Recurrent users (>3 prescriptions) (n=21,335)**	**Total NHS Tayside and Fife Health Board area population (n=785,800)**
Age in years (mean, SD)	54.2 ± 14.2	58.12 ± 15.64	n/a
Age group (years), n (%)			
0-20	99 (0.3)	58 (0.3)	174,194 (22.1)
21-40	4,230 (14.5)	2,888 (13.5)	192,263 (24.5)
41-60	12,109 (41.6)	9,133 (42.8)	216,421 (27.5)
61-80	10,149 (34.9)	7,400 (34.7)	163,957 (20.8)
80+	2,524 (8.7)	1,856 (8.7)	38,965 (4.9)
Gender, n (%)			
Female	18,231 (62.6)	13,334 (62.5)	404,085 (51.4)
Male	10,880 (37.4)	8,001 (37.5)	381,715 (48.6)
Health board, n (%)			
Tayside	15,233 (52.3)	11,240 (52.7)	415,470 (52.9)
Fife	13,878 (47.7)	10,095 (47.3)	370,330 (47.1)
Deprivation Index (SIMD)*, n(%)			
SIMD1 (most deprived)	6,907 (24.8)	5,358 (26.1)	143,157 (18.2)
SIMD2	6,344 (22.7)	4,796 (23.4)	139,032 (17.7)
SIMD3	5,438 (19.5)	3,893 (19)	159,478 (20.3)
SIMD4	5,893 (21.1)	4,156 (20.3)	192,578 (24.5)
SIMD5 (least deprived)	3,328 (11.9)	2,301 (11.2)	151,555 (19.3)
Rurality, n (%)			
Combined Large Urban and Other Urban:	19,452 (69.7)	14,448 (70.5)	516,885 (65.8)
Accessible small town and remote small town combined	3,627 (13.0)	2,611 (12.7)	102,734 (13.1)
Accessible rural and remote rural combined	4,831 (17.3)	3,445 (16.8)	166,182 (21.1)

*SIMD = Scottish Index of Multiple Deprivation, % calculated for SIMD and Rurality on complete data

Table 2. Co-prescribing of opioids and/or benzodiazepines with gabapentinoids in NHS Tayside & NHS Fife (2016), n (%) of all those prescribed gabapentinoid at least once)

	No. of Individuals*	Male**	Female**	P-value***
Gabapentinoids	29,111	10,880 (37.2)	18,231 (62.4)	-
Gabapentinoids + any opioids	14,574 (49.9)	5,442 (50.0)	9,132 (50.1)	NS
Gabapentinoids + benzodiazepines	7,823 (26.8)	2,635 (24.2)	5,188 (28.5)	<0.01
Gabapentinoids + opioids + benzodiazepines	4,986 (17.1)	1,732 (15.9)	3,254 (17.8)	<0.01
Gabapentinoids + opioids and/or benzodiazepines	17,411 (59.6)	6,345 (58.3)	11,066 (60.7)	<0.01
Gabapentinoids without co-prescription records of opioids and/or benzodiazepines	11,700 (40.1)	4,535 (41.7)	7,165 (39.3)	-

*% shown of co-prescribing within any gabapentinoid prescription

**% shown within male and female for co-prescribing

*** chi square test comparing % in males and females

Table 3. Socio-demographic characteristics of patients who received gabapentiniods prescriptions with and without co-prescribed opioids and/or benzodiazepines (2016)

	Gabapentinoids and co-prescriptions (n=17,411)	**Gabapentinoids prescriptions only (n=11,700)**	**p-value**
Age (mean, SD)	57.34±15.82	58.83±16.12	<0.0001
Age group, n(%)			
0-20	37 (0.2)	62 (0.5)	<0.01
21-40	2,681 (15.4)	1,549 (13.2)	
41-60	7,497 (43.1)	4,612 (39.4)	
61-80	5,743 (33.0)	4,406 (37.7)	
80+	1,453 (8.3)	1,071 (9.2)	
Gender, n(%)			
Female	11,066 (63.6)	7,165 (61.2)	<0.0001
Male	6,345 (36.4)	4,535 (38.8)	
Health board, n(%)			
Tayside	9,392 (53.9)	5,631 (48.1)	<0.0001
Fife	8,019 (46.1)	6,069 (51.9)	
Deprivation Index (SIMD), n(%)			
SIMD1 (most deprived)	4,447 (26.7)	2,460 (21.9)	<0.00001
SIMD2	3,914 (23.5)	2,430 (21.6)	
SIMD3	3,176 (19)	2,262 (20.1)	
SIMD4	3,362 (20.2)	2,531 (22.5)	
SIMD5 (least deprived)	1,763 (10.6)	1,565 (13.9)	
Rurality code, n(%)			
Combined Large Urban / other Urban	11707 (70.3)	7745 (68.8)	0.00613
Accessible small town / remote small town combined	2169 (13.0)	1458 (13.0)	
Accessible rural / remote rural combined	2786 (16.7)	2045 (18.2)	

*SIMD = Scottish Index of Multiple Deprivation.

Data are means ± standard deviation (SD) for continuous variables and counts (%) for categorical data. Univariate analysis was performed. P<0.05 taken as significant.

Table 4. The association between socio-demographic factors and co-prescription of opioids and/or benzodiazepines with gabapentinoids from Tayside and Fife in 2016

	Odds Ratio* (95%CI)	P-value
Age		
18-40 (2)	Reference category	
0-17 (1)	0.69 (0.57 - 0.82)	<0.001
41-60 (3)	0.99 (0.98 - 1.01)	0.672
61-80 (4)	0.95 (0.93 - 0.96)	<0.001
80+ (5)	0.96 (0.94 - 0.98)	0.004
Gender		
Female	Reference category	
Male	0.97 (0.96 - 0.98)	<0.001
Deprivation Index (SIMD)		
SIMD1 (most deprived)	Reference category	
SIMD2	0.97 (0.96 - 0.99)	0.0039
SIMD3	0.95 (0.93 - 0.96)	<0.001
SIMD4	0.94 (0.92 - 0.95)	<0.001
SIMD5 (least deprived)	0.90 (0.88 - 0.92)	<0.001

* Multivariate logistic regression analysis

SIMD = Scottish Index of Multiple Deprivation

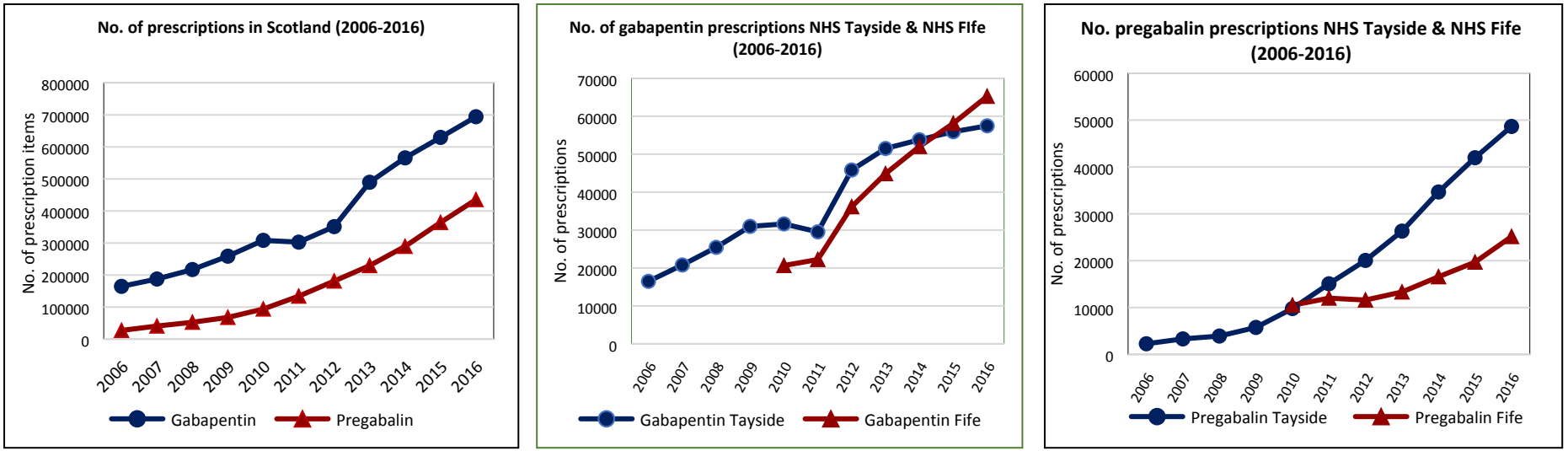

Figure 1. Trends in prescribing of pregabalin and gabapentin in Scotland, NHS Tayside and NHS Fife (2006 to 2016)

*Note: prescribing data for NHS Fife only available from 2010

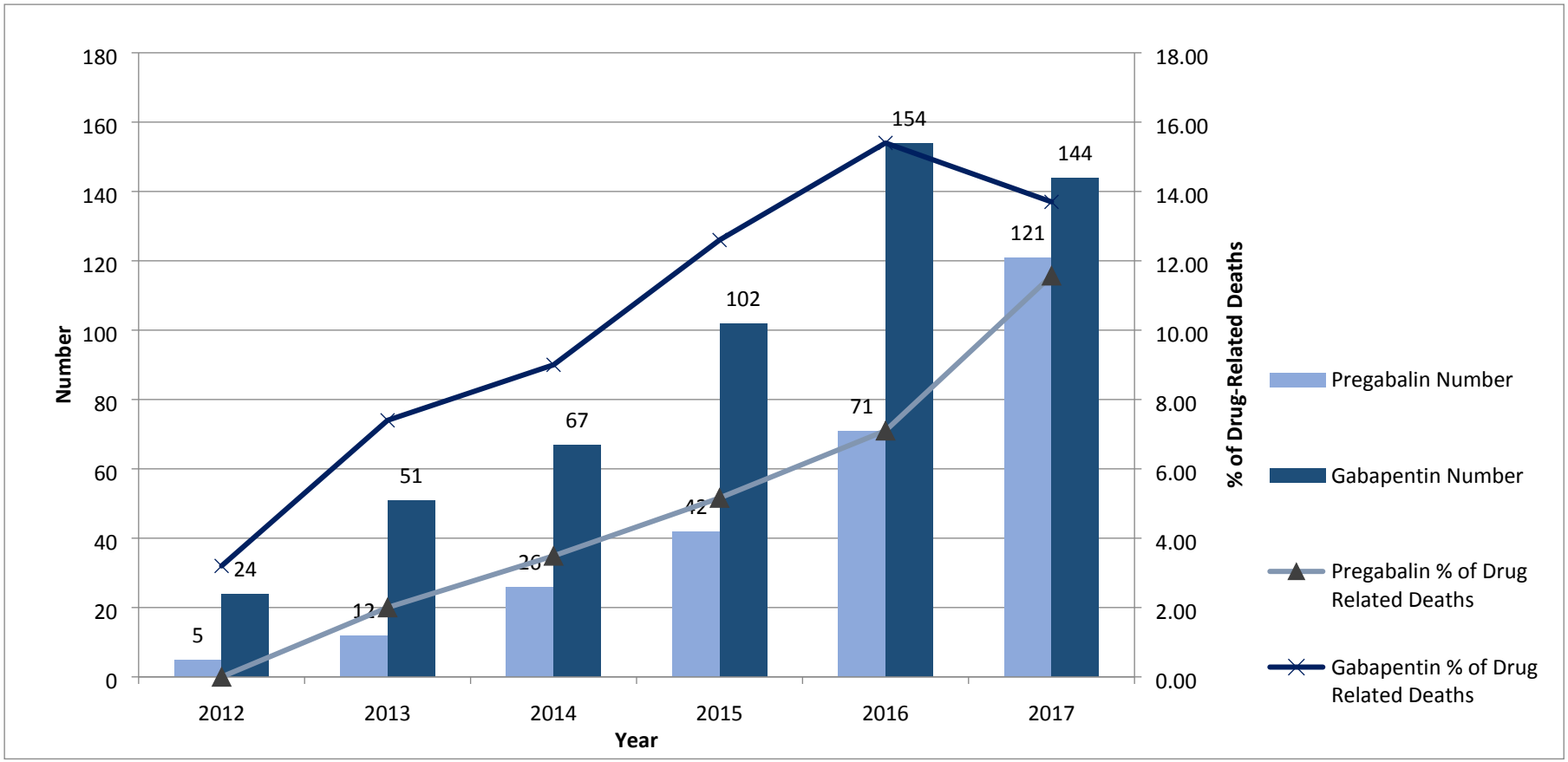

Figure 2a. Drug-related deaths where pregabalin and gabapentin were implicated in or potentially contributed to cause of death by number and percentage: Scotland 2012-2017¥

Footnote¥ Drug death, as defined by National Records of Scotland[23]

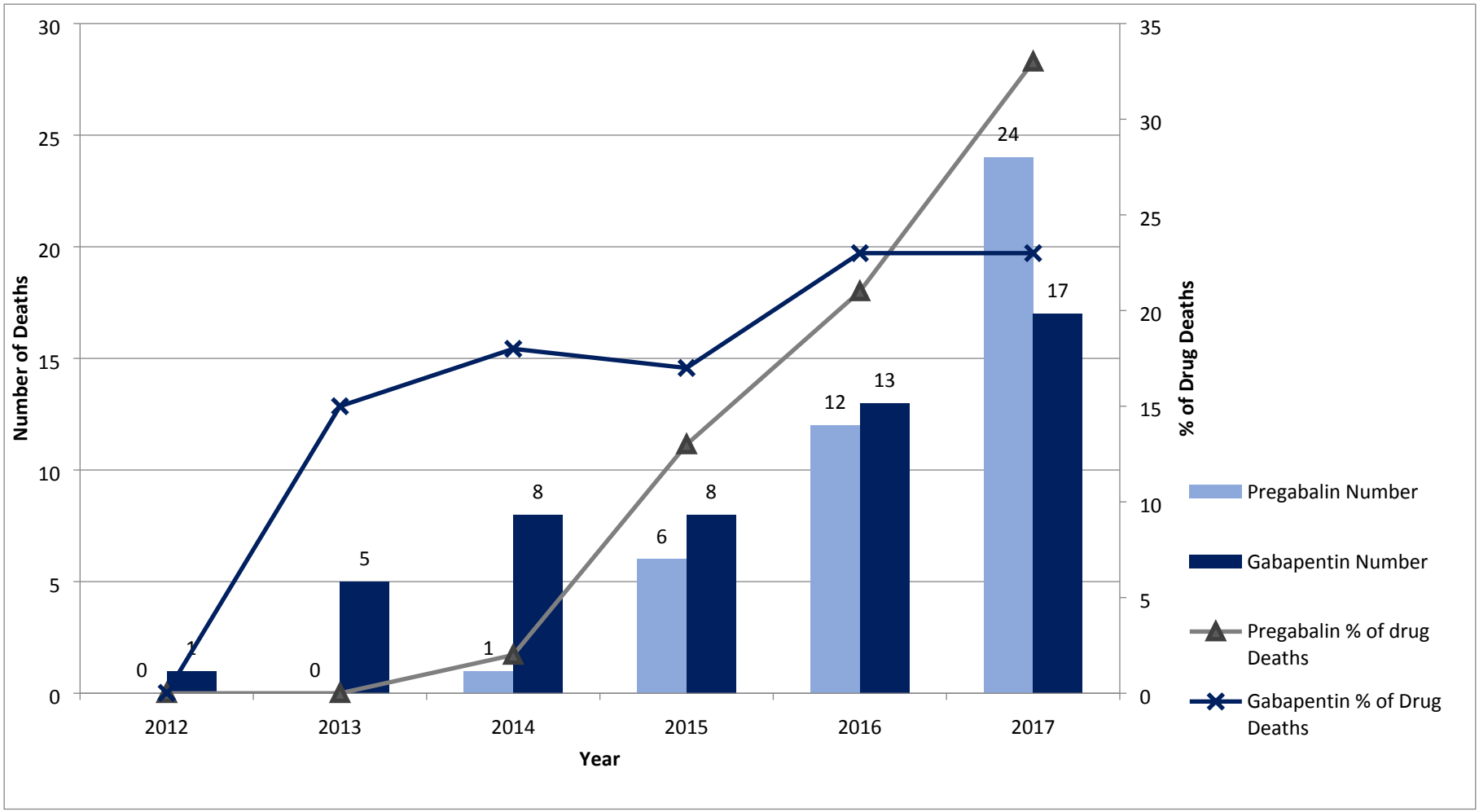

Figure 2b. Drug deaths where pregabalin and gabapentin were implicated in or potentially contributed to cause of death by number and percentage: Tayside 2012-2017[$]

Footnote[$] Drug death, as defined by the Tayside Drug Death Review Group[31] (see text)

Supplementary table 1. Definition of drug related deaths

Description	ICD-10 codes
Mental and behavioural disorders	
Due to drug use (excluding alcohol and tobacco)	F11- F16, F18-F19
Unspecified cause/disorder	F99
Accidental self-harm	
Poisoning by drugs, medicaments and biological substances	X40-X44
Poisoning, other or unspecified exposure	X49
Other or unspecified means	X58,X599
Intentional self-harm	
Poisoning by drugs, medicaments and biological substances	X60- X64
Poisoning, other or unspecified exposure	X69
Other or unspecified means	X83, X84
Assault by	
Poisoning by drugs, medicaments and biological substances	X85
Poisoning, other or unspecified exposure	X90
Other or unspecified means	Y08, Y09
Self-harm, undetermined intent	
Poisoning by drugs, medicaments and biological substances	Y10-Y14
Poisoning, other or unspecified exposure	Y19
Other or unspecified means	Y33, Y34
External cause	
Poisoning by drugs, medicaments and biological substances	T36- T50
Poisoning, other or unspecified exposure	T65.8, T65.9,
Other or unspecified means	T788,T789

https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/deaths/methodologies/deathsrelatedtodrugpoisoninginenglandandwalesqmi#methodology-background

https://www.nrscotland.gov.uk/files//statistics/drug-related-deaths/17/drug-related-deaths-17-pub.pdf

Supplementary table 2. The association between socio-demographic factors and recurrent use of gabapentinoids (>3 prescriptions) in NHS Tayside and Fife Health Board areas in 2016

	Estimated effect size	*S.E.*	*P-value*	*OR*	*95% CI. for OR*	
					Lower	*Upper*
Intercept	0.72	0.01	$<2\times10^{-16}$	2.03	1.71	2.37
Age						
0-17 (1)	-0.14	0.08	0.07	0.86	0.74	1.02
41-60 (3)	0.08	0.01	$<2\times10^{-16}$	1.08	1.06	1.10
61-80 (4)	0.06	0.01	1.6×10^{-12}	1.06	1.04	1.08
80+ (5)	0.07	0.01	1.1×10^{-10}	1.07	1.05	1.10
18-40 (2)	Reference category					
Gender						
Male	0.002	0.005	0.632	1.00	0.99	1.01
Female	Reference category					
Deprivation Index (SIMD)						
SIMD2	-0.02	0.01	0.007	0.97	0.96	0.99
SIMD3	-0.06	0.01	6.76×10^{-15}	0.94	0.92	0.95
SIMD4	-0.07	0.01	$<2\times10^{-16}$	0.93	0.91	0.94
SIMD5	-0.08	0.01	$<2\times10^{-16}$	0.92	0.89	0.93
SIMD1 (most deprived)	Reference category					

Supplementary Table 3. The comparison of age standardised mortality (per 100,000 persons) between Scotland and those prescribed a gabapentinoid at least once in NHS Tayside and Fife in 2016

Cause of death	Age standardised death rate - gabapentinoids population	Age standardised death rate - Scotland population	Relative risk (95% CI)	P-value
All-cause mortality	2454.1	1136.4	2.16 (2.08-2.25)	<0.001
Circulatory	313.9	305.9	1.03 (0.91-1.41)	0.64
Respiratory	148.5	195.3	1.32 (1.15-1.50)	<0.001

Supplementary Table 4. Drug deaths in Tayside in 2016 by gabapentinoid involvement

	Gabapentinoid implicated in cause of death (n=22)	Gabapentinoid not implicated in cause of death (n= 34)
Mean age (years)	37.2	40.2
Male n (%)	18 (82)	26 (76)
Deprivation Index (SIMD), n (%)		
SIMD 1 (most deprived)	14 (64)	18 (53)
SIMD 2	5 (23)	8 (23)
SIMD 3	2 (9)	5 (15)
SIMD 4	1 (5)	3 (9)
SIMD 5 (least deprived)	-	-

*Scottish Index of Multiple Deprivation (SIMD