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Pain

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 of ~7%. Concerns about increased 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 the Information Service Division, NHS Scotland were analysed for prescribing, sociodemographic, and mortality data from the Health Informatics Centre, University of Dundee. DRDs in which gabapentinoids were implicated were identified from National Records of Scotland and Tayside Drug Death Databases.

Results: From 2006 to 2016, the number of gabapentin prescriptions in Scotland increased 4-fold (164 630 to 694 293), and pregabalin 16-fold (27 094 to 435 490). In 2016 'recurrent users' (three or more prescriptions) had mean age 58.1 yr, were mostly females (62.5%), and were more likely to live in deprived areas. Of these, 60% were co-prescribed an opioid, benzodiazepine, or both (opioid 49.9%, benzodiazepine 26.8%, both 17.1%). The age-standardised death rate in those prescribed gabapentinoids was double that in the Scottish population (relative risk 2.16, 95% confidence interval 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%) of 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: benzodiazepine; drug diversion; drug-related death; gabapentinoid; mortality; opioid; prescribing; social deprivation

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Editor's key points

- Drug-related deaths have increased, and toxicology reports often implicate gabapentinoids.
- Drug-related deaths in which gabapentinoids were implicated were identified from the National Records of Scotland and Tayside Drug Death Databases.
- From 2006 to 2016, the number of gabapentin prescriptions in Scotland increased four-fold, particularly in females and those in deprived areas, with 60% co-prescribed an opioid, benzodiazepine, or both.
- The age-standardised death rate in those prescribed gabapentinoids was double the rate in the Scottish population.
- Increases in gabapentinoids contributing to cause of drug-related deaths were reported regionally and nationally.

Initially developed to treat epilepsy, gabapentinoid drugs (gabapentin and pregabalin) are also widely used for the treatment of neuropathic pain (for which they are licensed in the UK and elsewhere), migraine, and generalised anxiety disorder in adults (pregabalin only).[1] Chronic pain is common with a prevalence of 19% of the population in Europe,[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] North America,[12–14] and Europe.[15,16] The rate of patients newly treated with gabapentinoids has increased three-to four-fold since 2002,[9,12] as have the number of 'gabapentinoid-involved' visits to a doctor.[17] These increases cannot wholly be explained by the number of cases of neuropathic pain or other relevant conditions. It has been suggested that clinicians, seeking alternatives to prescribing opioids[18] and concerned about long-term nonsteroidal anti-inflammatory drug and coxib prescribing,[19] are responding by lowering the threshold for prescribing gabapentinoids for various types of pain, and prescribing is 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] 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 (DRDs) are of particular public health concern currently. Prescribed gabapentinoids have been associated with increased risk of suicidal behaviour, and unintentional overdose, injuries, road traffic accidents, and violent crime.[24] In Scotland, DRDs have doubled in the past decade, resulting in the highest rate recorded in the EU in 2018.[25] Gabapentin was implicated in 15.2% of these DRDs and pregabalin in 16.5%. This is a substantial increase compared with only 3% and <1% in 2012, respectively.[25] Drug use disorders are also a major contributor to health inequalities as they are the greatest cause of years lost as a result of 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 because of concerns about their misuse and the growing number of deaths associated with their misuse.[27,28] Scotland is recognised as having one of the most developed recording mechanisms for DRDs 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 11-yr period (2007–2016) and identify associated sociodemographic factors and co-prescribing information. Data from well-defined robust datasets are examined to determine factors associated with co-prescribing and with DRDs information.

Methods

Data sources

National prescribing data

The NHS in Scotland is administered through 14 geographical NHS Boards. The Prescribing Information System 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, part of NHS Scotland (http://www.isdscotland.org/). General practitioners account for >95% of community prescribing and capture from prescriptions is high at 98.7% for general practitioner prescribers.[29]

We examined national level data from the Information Services Division. 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 more than 10 yr 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 ~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 sociodemographic factors, co-prescribing, and mortality.
3. DRDs 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

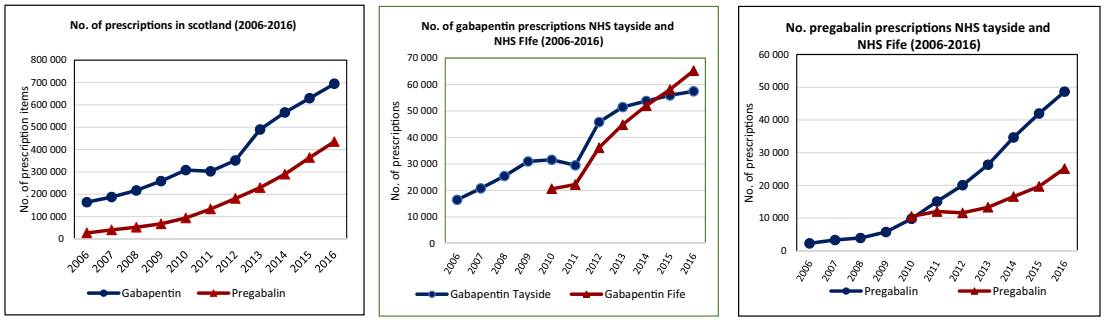

Fig 1. Trends in prescribing of pregabalin and gabapentin in Scotland, NHS Tayside, and NHS Fife (2006–2016). Prescribing data for NHS Fife only available from 2010.

toxicology reporting of gabapentin and pregabalin separately.

Individual prescribing data from NHS Tayside and NHS 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 ~780 000). This eHealth record linkage used a unique person identifier, the Community Health Index number. Data were linked between the following datasets: prescription medicines dispensed by community pharmacies, demographic data (age, gender, Scottish Index of Multiple Deprivation [SIMD], urban/rural categorisation of residence), and death records from General Records Office of Scotland. 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 1-yr 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 NHS 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 NRS categories. The standard population used to calculate age-standardised death rates was the 2013 European Standard Population. The European Standard Population is a theoretical population defined as having a particular distribution by age, which enables comparisons between different countries or populations.[31]

DRDs are identified using details from death registrations supplemented by toxicology information obtained from forensic pathologists, and are defined as deaths (intentional or unintentional) as a result of the effect of opioids, cannabinoids, sedatives or hypnotics, cocaine (or other stimulants), hallucinogens, or other psychoactive substances.[25] Deaths attributable to a complication of the immediate or short-term use of drugs listed above (e.g. bronchopneumonia as a result of heroin intoxication) are also considered DRDs. General Records Office of Scotland data included details of the underlying cause of death classified according to ICD-10 codes. DRDs are identified by the NRS using ICD-10 codes (Supplementary Table S1). NRS also reports DRDs 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 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 postmortem 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 DRDs.

Ethical approval

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

Table 1 Characteristics of patients in NHS Tayside and Fife Health Board areas prescribed gabapentinoids in 2016. SD, standard deviation; SIMD, Scottish Index of Multiple Deprivation, % calculated for SIMD and rurality on complete data.

	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 (yr) (mean, SD)	54.2 (14.2)	58.12 (15.6)	n/a
Age group (yr), *n* (%)			
0–20	99 (0.3)	58 (0.3)	174 194 (22.1)
21–40	4230 (14.5)	2888 (13.5)	192 263 (24.5)
41–60	12 109 (41.6)	9133 (42.8)	216 421 (27.5)
61–80	10 149 (34.9)	7400 (34.7)	163 957 (20.8)
80+	2524 (8.7)	1856 (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)	8001 (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)	6907 (24.8)	5358 (26.1)	143 157 (18.2)
SIMD2	6344 (22.7)	4796 (23.4)	139 032 (17.7)
SIMD3	5438 (19.5)	3893 (19)	159 478 (20.3)
SIMD4	5893 (21.1)	4156 (20.3)	192 578 (24.5)
SIMD5 (least deprived)	3328 (11.9)	2301 (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	3627 (13.0)	2611 (12.7)	102 734 (13.1)
Accessible rural and remote rural combined	4831 (17.3)	3445 (16.8)	166 182 (21.1)

Statistical analysis

Mainly descriptive analyses were conducted to examine 11-yr 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, benzodiazepines, or both in 2016. Continuous variables are presented as mean (standard deviation), and were analysed by independent *t*-test for difference in mean between groups. Categorical variables are presented as counts (%). 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 (RR) and 95% CIs were calculated for each age standardised mortality rate. We used a threshold of 5% ($P<0.05$) for statistical significance. All statistical analyses were conducted using IBM SPSS (**IBM** Corp., Armonk, N.Y., USA) 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 increased four-fold from 164 630 in 2006 to 694 293 in 2016, with greater increases in the number of pregabalin prescriptions (Fig. 1). In NHS Tayside, gabapentin prescriptions increased from 16 481 in 2006 to 57 472 in 2016 (3.5×) and in NHS Fife, there were 20 465 prescriptions issued in 2010, which increased to 65 241 in 2016 (3.2×). 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, 73.2% (*n*=21 335) were recurrent users with three or more dispensed prescriptions (Table 1). The mean age of recurrent users was 58.1 (15.6) yr, the highest proportion were women (62.5%), and they were more likely to live in areas of highest deprivation (SIMD quintile 1). The largest proportion of recurrent users lived in urban areas (70.5%).

Co-prescribing of opioids, benzodiazepines, or both

Co-prescribing was common, with almost 60% of those receiving gabapentinoids also prescribed an opioid, a benzodiazepine, or both 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 sociodemographic characteristics are shown in Tables 3 and 4. The mean age of the patients prescribed gabapentinoids along with opioids, benzodiazepines, or both was 57.3 (15.8) yr. Most of them were 41–60 yr ($P<0.01$), and there was a higher proportion of women compared with 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

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

	Number of individuals*	Male†	Female†	P-value‡
Gabapentinoids	29 111	10 880 (37.2)	18 231 (62.4)	–
Gabapentinoids + any opioids	14 574 (49.9)	5442 (50.0)	9132 (50.1)	NS
Gabapentinoids + benzodiazepines	7823 (26.8)	2635 (24.2)	5188 (28.5)	<0.01
Gabapentinoids + opioids + benzodiazepines	4986 (17.1)	1732 (15.9)	3254 (17.8)	<0.01
Gabapentinoids + opioids, benzodiazepines, or both	17 411 (59.6)	6345 (58.3)	11 066 (60.7)	<0.01
Gabapentinoids without co-prescription records of opioids, benzodiazepines, or both	11 700 (40.1)	4535 (41.7)	7165 (39.3)	-

* Percentage co-prescribing within any gabapentinoid prescription.
† Percentage within male and female for co-prescribing.
‡ χ^2 test comparing percentage in males and females.

significantly associated with older age (41–60 yr, OR 1.08 [95% CI 1.06–1.10]) and with living in more deprived areas (compared with SIMD 1 most deprived, SIMD 3, OR 0.94 [95% CI 0.92–0.95]) (Supplementary Table S2).

Deaths

In total, there were 1312 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 NHS Fife 2016: RR 2.16 (95% CI 2.08–2.25, *P*<0.001) and for deaths attributable to respiratory disease (RR 1.32, 95% CI 1.15–1.50, *P*<0.001), although not for deaths attributable to circulatory disease (RR 1.03, 95% CI 0.91–1.41, *P*=0.64) (Supplementary Table S3).

Drug-related deaths

There has been a steady increase in the number of DRDs in Scotland and in NHS Tayside where gabapentin and pregabalin were implicated in or potentially contributed to the cause of death (Fig. 2a and b), although the percentages are higher in Tayside compared with 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 postmortem 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

Table 3 Sociodemographic characteristics of patients who received gabapentinoids prescriptions with and without co-prescribed opioids, benzodiazepines, or both (2016). SD, standard deviation; SIMD, Scottish Index of Multiple Deprivation. Data are means (SD) for continuous variables and counts (%) for categorical data. Univariate analysis was performed. *P*<0.05 taken as significant.

	Gabapentinoids and co-prescriptions (*n*=17 411)	Gabapentinoids prescriptions only (*n*=11 700)	P-value
Age (yr) (mean, SD)	57.3 (15.8)	58.8 (16.1)	<0.0001
Age group (yr), *n* (%)			
0–20	37 (0.2)	62 (0.5)	<0.01
21–40	2681 (15.4)	1549 (13.2)	
41–60	7497 (43.1)	4612 (39.4)	
61–80	5743 (33.0)	4406 (37.7)	
80+	1453 (8.3)	1071 (9.2)	
Gender, *n* (%)			
Female	11 066 (63.6)	7165 (61.2)	<0.0001
Male	6345 (36.4)	4535 (38.8)	
Health board, *n* (%)			
Tayside	9392 (53.9)	5631 (48.1)	<0.0001
Fife	8019 (46.1)	6069 (51.9)	
Deprivation Index (SIMD), *n* (%)			
SIMD1 (most deprived)	4447 (26.7)	2460 (21.9)	<0.00001
SIMD2	3914 (23.5)	2430 (21.6)	
SIMD3	3176 (19)	2262 (20.1)	
SIMD4	3362 (20.2)	2531 (22.5)	
SIMD5 (least deprived)	1763 (10.6)	1565 (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)	

Table 4 Association between sociodemographic factors and co-prescription of opioids, benzodiazepines, or both with gabapentinoids from Tayside and Fife in 2016. CI, confidence interval; SIMD, Scottish Index of Multiple Deprivation.

	Odds ratio* (95% CI)	P-value
Age (yr)		
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.

substances to be found in toxicology of drug deaths at post-mortem (39 detections of pregabalin, gabapentin, or both), 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 yr *vs* 40.2 yr), more frequently male (82% *vs* 76%), and more likely to be living in areas of greater socioeconomic deprivation, although these differences were not statistically significant (Supplementary Table S4).

Discussion

Our 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, a benzodiazepine, or both (50% were co-prescribed an opioid and 27% a benzodiazepine only). Factors associated with gabapentinoid prescribing and co-prescribing include older age, female gender, and social deprivation. Overall rates of DRDs in Scotland have increased,[25] and DRDs where gabapentinoids are implicated or potentially contributed have also increased as a proportion of all DRDs. This 'contribution' is found in ~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.

The completeness rate of the prescribing data and community pharmacy dispensed prescriptions of gabapentinoids across Scotland (including NHS Tayside and Fife) are high.[29] This produced a large and comprehensive study population, minimising selection bias and enabling analysis of some individual level sociodemographic characteristics. This is an advantage compared with 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. The prescribing data lacked clinical details and we were unable to associate gabapentinoid prescriptions with specific diagnoses including neuropathic pain or epilepsy. Although we were able to determine those patients who received a prescription for gabapentinoids, opioids, or both and benzodiazepines in the same year, we are unable to confirm prescribing at the same time in the year.

Increasing 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 sociodemographic 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 1 yr (2017–2018) and 12.8% were prescribed opioids.[35,36] We found similar rates of gabapentinoid prescribing in Tayside (3.7%), and other research reported an opioid analgesic prescribing rate of 11% in Tayside and a rate of 18% of the population in Scotland.[11,37] The sociodemographic characteristics associated with gabapentinoid prescribing included age, with highest rates of prescribing found in those 40–60-yr-olds, of female gender, and with social deprivation. Similar findings have 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 15–22% in 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, alcohol, or all three.[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, pregabalin, or both were implicated in, or potentially contributed to the cause of death in ~1% of all DRDs[22] compared with data from 2018[25] where this figure was 13.7% of all DRDs. In Tayside, this figure is even higher at 23% (although this may in part be because of differences in drug death definitions). DRDs include

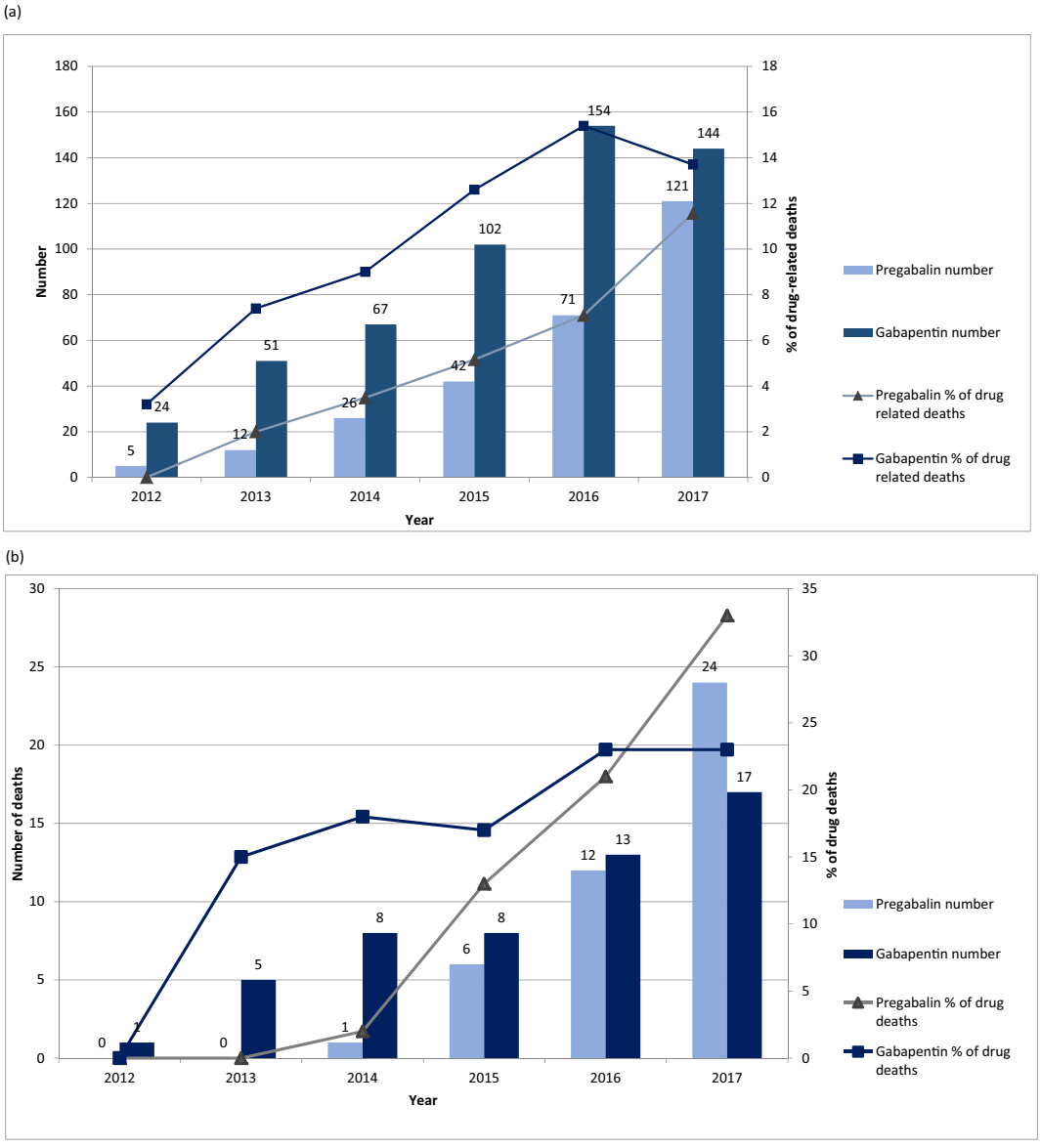

Fig 2. (a) Drug-related deaths where pregabalin and gabapentin were implicated in or potentially contributed to cause of death by number and percentage: Scotland 2012–2017. (Drug death, as defined by National Records of Scotland.[23]) (b) Drug deaths where pregabalin and gabapentin were implicated in or potentially contributed to cause of death by number and percentage: Tayside 2012–2017. (Drug death, as defined by the Tayside Drug Death Review Group[31]; see text.)

deaths that have occurred as a result of 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 in which gabapentinoids were 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, has similar underlying causal factors, or both.

Drug use disorders are the top 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 yr. This compares with the national average age of death in Scotland of 81 yr for females and 77 yr for males[41] and represents a gross health inequality in our population. The majority of DRDs occur in people who have experienced considerable life adversity, often from a young age. Factors that influence risk are multidimensional, 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 DRDs: atypical benzodiazepines (principally etizolam), gabapentinoids, and cocaine.[25] Each has different supply and distribution routes. Etizolam can be manufactured domestically, cocaine is imported, and both are illicit. 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 such 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 associated potential harms, dangerous co-prescribing, and death (including drug-related deaths). 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 drug-related deaths 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 drug-related deaths.[45]

Authors' contributions

Project conception and design for the prescribing data linkage: NT, BHS, LAC, HLH, PTD
Statistical analysis of the HIC data and age-standardised death rates: AV, YZ, PTD, JW
Statistical analysis of the national and Tayside DRDs data: EF, EM
Submission draft: NT
Critical revisions of the work for important intellectual content and final approval of the manuscript to be published: all authors

Declarations of interest

BHS is National Lead Clinician for Chronic Pain in Scotland. BHS and LAC 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, and is an editor of the *British Journal of Anaesthesia*. 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 are from the annual reports informed by the database which she maintains. NT, AV, HLH, JW, and ZY declare that they have no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bja.2020.05.017.

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