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SHORT COMMUNICATION

Fatalities associated with gabapentinoids in England (2004–2020)

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The gabapentinoids were reclassified as Schedule II medications and Class C drugs in the UK in 2019 due to their potential misuse. In this study we examined deaths following gabapentinoid use in England reported to the National Programme on Substance Abuse Deaths.

A total of 3051 deaths were reported (gabapentin: 913 cases; pregabalin: 2322 cases [both detected in 184 cases]). Prescribed and illicitly obtained gabapentinoids accounted for similar proportions of deaths (gabapentin illicit 38.0%, prescribed 37.1%; pregabalin illicit 41.0%, prescribed 34.6%). Opioids were co-detected in most cases (92.0%), and co-prescribed in a quarter (25.3%). Postmortem blood gabapentinoid concentrations were commonly (sub)therapeutic (65.0% of gabapentin cases; 50.8% of pregabalin cases). In only two cases was gabapentinoid toxicity alone attributed in causing death.

Gabapentinoids alone rarely cause death. Clinically relevant doses can, however, prove fatal, possibly by reducing tolerance to opioids. Doctors and patients should be aware of this interaction.

Gabapentinoid–opioid co-prescribing needs urgent revision.

KEYWORDS
drug-related death, gabapentin, gabapentinoid, opioid, pregabalin, toxicity, toxicology

1 | INTRODUCTION

The gabapentinoids, **gabapentin** and **pregabalin**, are indicated as treatments for neuropathic pain,[1] generalised anxiety and adjunctive treatment for seizures in the United Kingdom.[2] Whilst indicated specifically for neuropathic pain in adults,[3] they are increasingly used off-label for the treatment of other pain disorders[4,5]—a practice possibly driven by attempts to reduce the use of potentially addictive opioid analgesics.[6]

However, concerns around the non-medical use (so-called "misuse") of the gabapentinoids themselves are growing, as well as those pertaining to their iatrogenic dependence, diversion and toxicity.[7–17] In response, they were reclassified in the UK as Schedule II medications and Class C drugs in April 2019.[18,19] Mixed methods qualitative and pharmacological research indicates that co-administration of a gabapentinoid and an opioid reverses opioid tolerance,[20,21] which increases their desirability for use in combination and to which the populations who misuse opioids are particularly vulnerable.[11] This also implies potential for toxicity via drug–drug interaction (note: although misuse can relate to toxicity, in that toxicity may result from taking higher than prescribed

The authors confirm that the Principal Investigator for this paper is Caroline S. Copeland. She had direct responsibility for the data (note: patient consent was not applicable to this study as all subjects were deceased).

quantities of medication, the two are separate). Furthermore, preclinical research suggests that gabapentinoid co-administration reduces effectiveness of naloxone reversal.[20] This has implications for the co-prescribing of opioids and gabapentinoids, particularly for patients who are prescribed opioid substitution therapy for opioid dependence,[22,23] as well as the focus of harm minimisation information given to patients.

In this study we have explored deaths in England where gabapentinoids were detected at postmortem, with the aim of informing clinical practice for the prescribing of these medications and concomitant patient management to reduce fatal outcomes.

What is already known about this subject

- The gabapentinoids, gabapentin and pregabalin, are indicated for treating neuropathic pain and generalised anxiety disorder, and as an adjunct for treating seizures, in the UK.
- They also have a growing reputation as possessing misuse potential, likely related to their reported ability to reduce tolerance to opioids.

What this study adds

- Gabapentinoids alone rarely cause death, but clinically relevant doses can prove fatal, possibly due to reducing tolerance to opioids.
- In 25.3% of gabapentinoid deaths in England, the gabapentinoid had been co-prescribed with an opioid.
- Doctors and patients should be aware of this interaction, and gabapentinoid–opioid co-prescribing needs urgent revision.

2 | METHODS

2.1 | National Programme on substance abuse deaths (NPSAD)

NPSAD receives information from coroners in England on a voluntary basis on deaths related to drugs. Toxicology tests are requested at the discretion of the coroner and/or pathologist, dependent upon individual case circumstances. Coroners report a death to NPSAD if one or more psychoactive substance(s) is detected and/or directly implicated in causing death, or if the decedent had a history of drug (mis)use.

The King's College London Biomedical & Health Sciences, Dentistry, Medicine and Natural & Mathematical Sciences Research Ethics Sub-Committee confirmed (November 2020) that NPSAD does not require ethics review as all subjects are deceased.

2.2 | Case identification

A range of documents are typically contained in coronial inquest files: statements from witnesses, family and friends; General Practitioner (GP) records (if the deceased is registered with one); first responder reports (e.g., police, emergency services); hospital reports; psychiatric and substance abuse team reports; postmortem and toxicology reports.

Relevant cases reported to NPSAD from England as of 1 November 2021 were identified by searching the postmortem drug fields for the coded terms corresponding to gabapentin and pregabalin.

2.3 | Data analysis

2.3.1 | Software

Data analysis and statistics (Student's *t*-test; Chi-squared) were performed using IBM® SPSS™ Statistics for Windows version 27 and Microsoft Excel 365.

2.3.2 | 2020 Projection

There is a time delay between death and coronial inquest conclusion. Based on jurisdiction reporting trends, further deaths occurring in 2020 are anticipated to be reported to NPSAD, the number of which has been projected. Such projections have been made previously using NPSAD data[24,25] which upon re-analysis proved accurate.

2.3.3 | Cause of death

Causes of death are categorised by coroners, as follows:

Cause 1a: The immediate cause of death (and underlying if no 1b or 1c cited).
Cause 1b: Any disease/circumstances underlying Cause 1a.
Cause 1c: Any disease/circumstance underlying Cause 1b.
Cause 2: Any disease/circumstance that did not cause the death but contributed in some way.

Underlying cause of death was identified using these criteria.

2.3.4 | Method of obtainment

GP summaries and hospital records were used to categorise cases by gabapentinoid source: prescribed cases were those with a

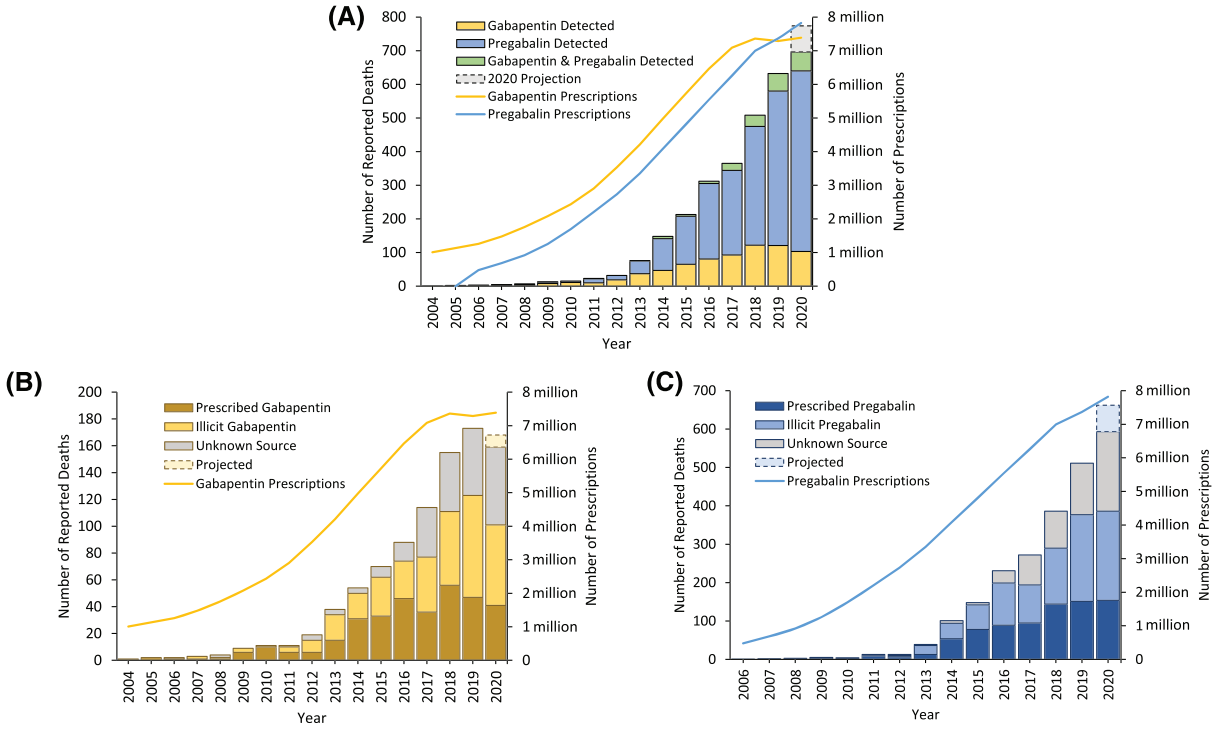

FIGURE 1 (A) Total number of deaths reported to NPSAD from England with gabapentin and/or pregabalin detected at postmortem. Further deaths occurring in 2020 are anticipated to be received (see Section 2.2). The secondary y-axis shows the number of General Practitioner prescriptions for prescribed gabapentinoids in England by year.[26] Detection of deaths with (B) gabapentin and (C) pregabalin delineated by source of obtainment

gabapentinoid prescription; illicit cases those where prescribing status was known but did not list a gabapentinoid; unknown cases were those where prescribing history was not provided.

2.3.5 | Prescribing data

Prescribing data were extracted from OpenPrescribing.net.[26]

3 | RESULTS

There were 3051 deaths with gabapentinoid detection: 913 cases with gabapentin (29.9%), 2322 cases with pregabalin (76.1%), 184 cases with both co-detected (6.0%). The first death with gabapentin detected occurred in 2004, and with pregabalin in 2006.

The number of deaths following gabapentinoid use has increased (Figure 1A): 8.9% of all NPSAD reports in 2014 detected a gabapentinoid, rising to 32.3% in 2020. Whilst more gabapentin prescriptions were issued 2004–2019, deaths related to pregabalin have been in the significant majority since 2014 (68.2% of cases in 2014 [$n = 101/148$] rising to 85.2% of cases in 2020 [$n = 593/696$]; all $P < .05$). Gabapentin and pregabalin were illicitly obtained in 38.0% ($n = 347/913$) and 41.0% ($n = 951/2322$; Figures 1B and 1C) of cases, respectively, and had been prescribed in comparable proportions of cases (37.1% of gabapentin cases [$n = 339/913$]; 34.6% of pregabalin cases [$n = 803/2322$]; Figures 1B and 1C).

Opioids were co-detected with a gabapentinoid in 92.0% of cases (total cases [$n = 2808/3051$]; 91.3% of gabapentin cases [$n = 834/913$]; 92.8% of pregabalin cases [$n = 2154/2322$]). **Alcohol** was co-detected in a significantly smaller proportion of cases (24.5%, $n = 746/3051$, $P < .01$). A total of 772 decedents (25.3%) were co-prescribed a gabapentinoid and an opioid, including 11 decedents co-prescribed an opioid and both gabapentinoids. **Methadone** was the most commonly co-prescribed opioid (Table 1). The opioid prescribing rate was lower when considering all cases, but trends in opioid type are complementary to trends in cases where gabapentinoids were prescribed (Table 1).

Acute drug toxicity was deemed the underlying cause of death in most cases (92.8% of gabapentin cases [$n = 847/913$]; 95.1% of pregabalin cases [$n = 2209/2322$]), with the detected gabapentinoid implicated in causing death in approximately half of cases (49.2% of gabapentin cases [$n = 449/913$]; 54.9% of pregabalin cases [$n = 1274/2322$]). The implication rates of co-detected opioids were significantly higher (90.4% [$n = 754/834$] and 93.7% [$n = 2019/2322$] of gabapentin- and pregabalin-related cases, respectively; both $P < .01$). Death was deemed unintentional in 85.4% ($n = 779/913$) and 91.3% ($n = 2119/2322$) of gabapentin and pregabalin cases, respectively, with a conclusion of suicide reached in 9.7% ($n = 89/913$) and 5.3% ($n = 123/2322$) of respective cases.

TABLE 1 Cases with a gabapentinoid and at least one opioid co-prescribed

	Prescribed		
	Gabapentin cases ($n = 339$)	Pregabalin cases ($n = 803$)	All cases ($n = 3051$)
Any opioid prescribed[a]	58.7% ($n = 230$)	51.0% ($n = 480$)	36.5% ($n = 1115$)
Buprenorphine	1.2% ($n = 4$)	4.1% ($n = 33$)	2.4% ($n = 73$)
Codeine	15.9% ($n = 54$)	13.2% ($n = 106$)	7.0% ($n = 213$)
Dihydrocodeine	9.4% ($n = 32$)	5.7% ($n = 46$)	3.2% ($n = 97$)
Fentanyl	3.8% ($n = 13$)	3.0% ($n = 24$)	1.7% ($n = 52$)
Methadone	13.2% ($n = 45$)	20.3% ($n = 163$)	14.4% ($n = 440$)
Morphine	17.4% ($n = 59$)	13.9% ($n = 112$)	7.5% ($n = 230$)
Oxycodone	10.0% ($n = 34$)	4.7% ($n = 38$)	2.9% ($n = 89$)
Tramadol	15.6% ($n = 53$)	8.7% ($n = 70$)	4.9% ($n = 151$)
Other opioid	0.3% ($n = 1$)[b]	0.6% ($n = 5$)[c]	0.2% ($n = 7$)[d]

[a]Will sum to greater than the total number of cases as multiple opioids prescribed in some cases.
[b]Meptazinol ($n = 1$).
[c]Dipipanone ($n = 1$), meptazinol ($n = 2$), tapentadol ($n = 2$).
[d]Dipipanone ($n = 2$), meptazinol ($n = 3$), tapentadol ($n = 2$).

TABLE 2 Postmortem blood concentrations of detected gabapentin (A) and pregabalin (B). Gabapentin detections were quantified in postmortem blood samples in 592 cases, and pregabalin detections in 1666 cases

A	<2 mg/L Subtherapeutic	2–24 mg/L Therapeutic	25–37 mg/L Toxic	≥38 mg/L Fatal
Gabapentin administered alone	–	0.2% ($n = 1$)[a]	–	–
Gabapentin polysubstance use including opioids	12.2% ($n = 72$)	47.0% ($n = 278$)	11.0% ($n = 65$)	20.6% ($n = 122$)
Gabapentin polysubstance use excluding opioids	1.7% ($n = 10$)	4.1% ($n = 24$)	1.5% ($n = 9$)	1.9% ($n = 11$)
B	**<2 mg/L Sub-therapeutic**	**2–10 mg/L Therapeutic**	**11–69 mg/L Toxic**	**≥70 mg/L Fatal**
Pregabalin administered alone	–	–	0.1% ($n = 1$)[a]	–
Pregabalin polysubstance use including opioids	12.1% ($n = 202$)	34.5% ($n = 574$)	41.3% ($n = 688$)	4.6% ($n = 76$)
Pregabalin polysubstance use excluding opioids	1.1% ($n = 19$)	3.1% ($n = 51$)	2.8% ($n = 46$)	0.5% ($n = 9$)

[a]Likely in the fatal range at time of death (see Section 3: Postmortem levels).

Blood concentration reference ranges for gabapentin and pregabalin are presented in Table 2A and 2B. Sixty-five per cent ($n = 385/592$) of cases with gabapentin quantifications and 50.8% ($n = 846/1666$) of cases with pregabalin quantifications, correlate with concentrations relevant to (sub)therapeutic dosing (Tables 2A and 2B). On average, blood concentrations were higher in cases where gabapentinoids were implicated in causing death (gabapentin postmortem only median 9.0 mg/L, interquartile range [IQR] 15 mg/L, range 0.1–284.0 mg/L; gabapentin-implicated median 22.0 mg/L, IQR 42.3 mg/L, range 0.01–702.0 mg/L; pregabalin postmortem only median 6.0 mg/L, IQR 9.0 mg/L, range 0.03–118.0 mg/L, pregabalin-implicated median 14.0 mg/L, IQR 21.4 mg/L, range 0.03–1305.0 mg/L), with pregabalin, on average, detected at lower blood concentrations than gabapentin.

In two cases a gabapentinoid had been taken alone and was cited as the immediate and underlying cause of death. In one case 17.0 mg/L gabapentin was detected in a blood sample collected 39 hours post admission, and in the other case a postmortem concentration of 30.1 mg/L pregabalin was found. In this second case, the time between pregabalin administration and death is unknown as the person was found dead.

Decedents prescribed gabapentinoids were on average older (44.9 years old ± 10.3) than those who obtained them illicitly (42.1 years old ± 10.4; $P < .01$). Males represent a larger proportion of deaths (62.5% of prescribed cases [$n = 708/1132$]; 70.5% of illicit cases [$n = 867/1230$]). A large proportion of decedents were known to use drugs (63.6%; $n = 1940/3051$).

4 | DISCUSSION

Despite their rescheduling in April 2019,[18,19] deaths following gabapentinoid use persist.[15] Opioids were often co-detected, and in a quarter of deaths both compounds had been co-prescribed. Gabapentinoid concentrations were commonly in the therapeutic range, suggesting a significant component of gabapentinoid toxicity

relates to their drug–drug interaction with opioids,[20,21] rather than basic toxicity from overdosing.

Similar proportions of deaths resulted following prescribed and illicitly obtained gabapentinoid use. Despite being contraindicated,[2] an increasing number of gabapentinoid–opioid co-prescriptions are being issued.[27] This may be driven by initiatives to reduce opioid prescribing,[6] the prescribing of pregabalin for anxiety,[28] or their use in treating opioid dependence,[29] despite a lack of long-term efficacy evidence and concerns about harms.[28]

Vigilance in gabapentinoid prescribing is also needed to reduce opportunity for their misuse and diversion, as a black market is well established.[30] Dispensing restrictions that were effective in reducing the mortality from illicitly obtained methadone in the 1990s[31] should be considered, especially where patients already attend pharmacies for directly supervised consumption of opioid substitution treatment (OST).

Opioid–gabapentinoid co-administration is common[14–16,30,32–34] with a reported 70% prevalence in individuals receiving OST.[7,8] Healthcare professionals working with people who use opioids should explain the elevated risk of death with concurrent use of gabapentinoids—even if taken as prescribed[20]—and encourage them to reduce or stop taking them. The omission of gabapentinoids as a cause of death when detected alongside opioids may reflect a lack of awareness of the drug–drug interaction between gabapentinoids and opioids, or perhaps a view that the presence of opioids is sufficient to explain demise.

In some cases with therapeutic gabapentinoid levels, supratherapeutic concentrations may have occurred prior to death within the toxic/fatal ranges. However, therapeutic doses have been detected in other studies examining opioid-gabapentinoid death,[14,17,30,32–38] lending cumulative weight to the proposition that some of the toxicity of the gabapentinoids relates to their drug–drug interaction with opioids rather than their intrinsic pharmacology. Healthcare professionals should consider rationalising opioid–gabapentinoid co-prescribing and explain the risks to patients. Of note, the new NICE Chronic Pain Guidelines state that opioids and gabapentinoids should not be initiated for chronic primary pain and that patients already taking them should be reviewed.[39]

Only two deaths were attributable to sole gabapentinoid toxicity, and these involved relatively high concentrations. One decedent had a gabapentin level of 17 mg/L, collected ~39 hours post-admission. Assuming a 10 hour half-life estimate,[40] the gabapentin level at admission could have exceeded 100 mg/L. In the other case, 30.1 mg/L pregabalin was detected in a postmortem blood sample. Similarly, the actual concentration of ingested pregabalin was likely substantially higher. Indeed, case reports attributable to gabapentinoid overdose alone have detected higher postmortem levels.[30,41–43]

Pregabalin seems preferred for recreational use,[14,34] perhaps because it is absorbed more quickly and has greater bioavailability than gabapentin.[44,45] This is reflected in the postmortem blood levels: on average, lower concentrations of pregabalin were detected in fatalities indicating higher potency and potential for toxicity (note: the gabapentinoids do not undergo extensive postmortem redistribution due to their low volumes of distribution[44,46]). This may account for the higher number of deaths following pregabalin use than gabapentin, despite pregabalin being prescribed less often, in a demographic reflective of gabapentinoid misuse trends (majority male with a high incidence of substance misuse history[14,17,32,34]).

5 | LIMITATIONS

As toxicology testing requests for the gabapentinoids have increased in response to an awareness of their potential toxicity, part of the increase in NPSAD reporting is potentially an artefact of improved gabapentinoid detection. However, as NPSAD receives voluntary reports and coronial investigations with fully comprehensive toxicology screens are not carried out for all deaths,[47] the figures presented here almost certainly under-represent the true number of deaths following gabapentinoid use that has occurred in England. Interpretation of postmortem toxicology data is also limited by the variation in source (e.g., femoral or peripheral blood) and the timepoint at which blood sampling was performed. Cause and manner of death is determined by the coroner or jury and is subjective based upon the amount of available evidence. Further analysis accounting for confounding variables is required before additional comment can be made upon suicide rates.[48] Data pertaining to decedent demographics (e.g., prescribing status, known history of substance use) was not always provided.

6 | CONCLUSION

The drug–drug interaction between gabapentinoids and opioids may be of at least equal importance to misuse in explaining gabapentinoid toxicity. Doctors should be aware of this interaction and patients informed of the risk. Interventions to reduce continued prescribing of gabapentinoids in patients who also use or are prescribed opioids, such as the single consultation or letter-based approaches shown to be effective in reducing benzodiazepine prescribing,[49] should be explored.

6.1 | Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, and are permanently archived in the Concise Guide to PHARMACOLOGY 2019/20.

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COMPETING INTERESTS

D.T. reports personal fees from Lundbeck, and grants and personal fees from Janssen, outside the submitted work. C.S.C. reports personal fees from Transport Research Laboratory (TRL), outside the submitted work. None of the other authors have interests to declare.

CONTRIBUTORS

N.J.K. conceptualisation, visualisation, writing – original draft. C.T.C. software, validation, formal analysis, investigation, writing – review and editing. R.S. validation, formal analysis, investigation, writing – review and editing. H.B. validation, formal analysis, investigation, writing – review and editing. B.D.W. conceptualisation, investigation, writing – review and editing. D.T. conceptualisation, writing – review and editing. C.S.C. conceptualisation, methodology, software, validation, formal analysis, investigation, resources, data curation, writing – original draft, visualisation, supervision, project administration.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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