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Impact of gabapentinoids' reclassification policy and COVID-19 on gabapentinoids' utilization pattern and their associated mortality in Scotland and Northern Ireland: a segmental regression analysis

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ABSTRACT

Background: Gabapentinoids are commonly used for neuropathic pain but are increasingly linked with misuse/mortality. In 2019, the UK reclassified them as Schedule 3 controlled drugs. The onset of the COVID-19 pandemic created additional uncertainty regarding their utilization. We aimed to examine the impact of reclassification and COVID-19 on gabapentinoid utilization and related mortality in Scotland and Northern Ireland (NI).

Research design/methods: A population-based, cross-national study was conducted using prescribing datasets (April/2018–February/2025). Utilization was measured as total items dispensed per 1,000 inhabitants and defined daily doses per 1,000 inhabitants/day. Gabapentinoid-related mortality data were analyzed in parallel. Segmented regression assessed changes in trends following the 2019 reclassification and two COVID-19 lockdowns.

Results: Overall utilization was higher in Scotland than NI. In Scotland, pregabalin prescribing significantly increased over the study period, while NI demonstrated a decline, largely attributable to formulary restrictions. Neither reclassification nor pandemic lockdowns were associated with statistically significant changes in prescribing patterns. Mortality rates showed no significant correlation with utilization in either country.

Conclusions: Gabapentinoid utilization does not appear to have been significantly affected by the reclassification or by COVID-19. Cross-national differences underscore the influence of formulary guidance, highlighting the need for harmonized policies/patient-level research to inform safe prescribing.

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1. Introduction

Gabapentinoids (gabapentin and pregabalin) are a drug class functioning in the central nervous system (CNS) by binding to the alpha-2-delta subunit of calcium channels, causing a decrease in calcium influx [1], thus inhibiting the CNS and causing mainly analgesic, anticonvulsant and anxiolytic effects. Gabapentinoids are indicated only for epilepsy, central and peripheral neuropathic pain, menopausal symptoms in patients with cancer, multiple sclerosis symptoms, motor neuron diseases, and generalized anxiety disorder in the UK [2]. However, they are also commonly prescribed off-label for multiple pain indications, mainly for chronic non-cancer pain, with a lack of sufficient evidence, which may have aggravated the misuse problem [1,3,4].

It is now globally acknowledged that gabapentin and pregabalin are misused, abused, and taken for recreational purposes, often after taking more than the maximum daily dose [1,3–6]. The increasing misuse of gabapentinoids is primarily attributed to their psychoactive and euphoric effects, along with their widespread availability in clinical practice. Their perceived safety compar with opioids – owing to lower toxicity and fewer fatal overdoses – may further contribute to their misuse by creating a false sense of lower risk [1,4]. To achieve quicker effects, some people might use alternative routes of administration other than the oral route, including intravenous, rectal or by emptying the capsule content into a pouch and administering it, leading to increased quantities used [5]. While both pregabalin and gabapentin have a modest efficacy overall, pregabalin has demonstrated more consistent dose–response effects and greater bioavailability at lower doses compared with gabapentin [7–10]; hence, it requires lower doses to obtain the euphoric phase [4]. Additionally, conservative figures indicate that unnecessarily prescribed CNS drugs could have cost the National Health Service (NHS) England up to around £560,000,000 annually between 2015 and 2018, with gabapentinoids alone

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accounting for around 28% of that cost [11]. Furthermore, there is global evidence of an increase in gabapentinoid-related deaths [4,12], including the UK. Moreover, utilization of gabapentinoids tripled between 2010 and 2019 in the UK [6]. It is also suggested that deaths related to gabapentinoids reached around 80 per one million inhabitants in Scotland, and over 30 in Northern Ireland (NI) [6]. For comparison, opioid-related deaths were estimated at approximately 280 per one million inhabitants in Scotland and fewer than 150 in NI, underscoring the relative but growing contribution of gabapentinoids to drug-related mortality [6]. This problem led to some measures being taken in the UK.

In April 2019, the UK government reclassified gabapentinoids as Schedule 3 controlled drugs [13]. Specific restrictions for Schedule 3 prescriptions compared to Schedule 4 include the prescriber's address needing to be in the UK, no repeated prescriptions, requisition forms to be completed and, most importantly, the drugs not being available under the emergency supply scheme [14].

Another major event possibly impacting gabapentinoid use, similar to many other medication classes, is the COVID-19 pandemic. It is speculated that the pandemic caused a change in analgesic and gabapentinoid utilization, especially when people were staying at home during lockdowns and the consequences this isolation may have led to for patients using gabapentinoids [15,16]. A prospective German study found that gabapentinoid use was significantly higher after the pandemic in 2021 compared to 2018 [17]. One study noted a drop in prescribing gabapentinoids in primary care in the first five months after the reclassification in the UK [8], but it used the Clinical Practice Research Datalink (CPRD) as the data source, which represents under 20% of UK's population, and sometimes does not include Scotland or Wales depending on the dataset used [8,18], while no similar studies were found in Scotland or NI. Also, the study was only up to few months after the reclassification in September 2019 and did not measure long-term impact. Several UK studies have previously analyzed prescribing trends following the 2019 reclassification of gabapentinoids [8,19,20]. However, to date no study has systematically examined the long-term impact of this reclassification policy, along with COVID-19 pandemic, using comprehensive, population-level prescribing data linked to mortality outcomes across multiple UK jurisdictions. The present study addresses this gap by analyzing national data for Scotland and NI up to 2025, providing the most recent population-based assessment of gabapentinoid utilization and related mortality to date. Moreover, long-term effects of high utilization may include an increased possibility of gabapentinoid-related hospitalization [1], increased risk of dependence on gabapentin, a higher incidence rate of adverse effects and increased healthcare costs. Therefore, there is a need to study gabapentinoid utilization in previous years, starting before the reclassification, to understand its impact, along with the potential impact of the COVID-19 lockdown on utilization. Furthermore, the main hypotheses of the study are that the reclassification had decreased the utilization. Also, utilization was expected to increase during the pandemic, as a result of isolation, stress and mental problems relevant to them, especially anxiety.

The aim of this study was to investigate changes in gabapentinoid utilization over time, and to examine the potential impact of the 2019 reclassification and the COVID-19 pandemic on prescribing patterns in primary care across Scotland and NI. The study further explored the association between gabapentinoid utilization and gabapentinoid-related mortality. The findings are intended to inform strategies for optimizing gabapentinoid prescribing and to provide evidence to guide potential recommendations or modifications to clinical guidelines that support safer and more appropriate use.

2. Methodology

2.1. Study design and data sources

This was a repeated cross-national study using prescription cost analysis datasets in Scotland and NI general practices [21,22]. These publicly available, aggregated datasets capture all prescriptions dispensed in primary care anonymously, so no ethical approval, permission, or patient consent was required. Details included are drug name, number of items dispensed, and quantities supplied. The study period extended from April 2018 – one year prior to the reclassification of gabapentinoids in April 2019 – to February 2025, thereby encompassing both the March 2020 and October 2020 COVID-19 lockdowns [23]. Previous studies have highlighted utilization trends in earlier period of time, which can be used to provide broader trend of utilization [6]. A retrospective, population-based, cross-national design was chosen to enable assessment of long-term changes in gabapentinoid utilization at the national level. This design permits comprehensive evaluation of prescribing and mortality trends across Scotland and NI using routinely collected administrative datasets. Such an approach is well established in pharmacoepidemiology for evaluating the real-world impact of policy changes and public health events on medication use while avoiding the need for individual consent [24,25].

2.2. Study population and study outcomes

All formulations of gabapentin and pregabalin prescribed in Scotland and NI were included, based on British National Formulary section 4.8 [2]. Study outcomes were changes in gabapentinoid utilization patterns before and after the studied time periods, and mortality rates related to them. Gabapentinoid utilization was measured using two metrics, namely total items dispensed per 1,000 inhabitants (TID) and defined daily doses (DDD) per 1,000 inhabitants per day (DID) for both total gabapentinoids, gabapentin and pregabalin. DDD refers to the average adult maintenance dose used to treat the common indications for the drug [26]. The total number of items dispensed refers to the number of prescription items issued per 1,000 inhabitants, irrespective of pack strength or size and was summed for each drug monthly, then divided by the country's mid-year population [27,28] and multiplied by 1,000 to give TID. Simultaneously, for DID, the total quantity of each drug's strength was multiplied by its respective strength to calculate the total quantity (in milligrams) dispensed, which was then divided by the drug's DDD [29]. The total DDD was then multiplied by 1,000 and divided by the mid-year population

and the corresponding number of days in the month to obtain DID. Both TID and DID were used to provide complementary perspectives on utilization trends. While DID enables standardized comparison, TID captures dispensing frequency and helps identify behavioral or logistical changes in prescribing. Gabapentinoid-related death data were also used to extracted to assess the association between utilization and mortality. Mortality records are presented by year, meaning they were compared against the yearly average of TID and DID [30,31]. According to respective national statistics agencies gabapentinoid-related deaths are when gabapentinoids are found in the body at the time of death [30] and/or if mentioned in the death certificate as drug-poisoning, drug-abuse or drug dependence [31].

2.3. Data analysis

Change in prescription pattern overtime was analyzed using descriptive statistics, including absolute and relative change and time trend analysis using linear regression. Then segmented regression analysis of interrupted time series was applied [32], to assess the impact of the three interventions, namely: reclassification in April 2019 (intervention 1); the first COVID-19 national lockdown in March 2020 (intervention 2); and the second COVID-19 national lockdown in November 2020 (intervention 3). Seven coefficients were assessed and reported for the segmented regression, including: baseline trend (β1), level change immediately after intervention 1 (β2), time trend after intervention 1 (β3), level change immediately after intervention 2 (β4), time trend after intervention 2 (β5), level change immediately after intervention 3 (β6) and time trend after intervention 3 (β7). Then Pearson coefficient was used to study the correlation between mortality related to gabapentinoids and its utilization. Results were presented as regression coefficients with their p-value and 95% confidence interval (95% CI). A 12-month pre-intervention period was selected to provide an appropriate baseline for estimating level and slope changes while minimizing the influence of older prescribing patterns less relevant to current clinical practice. The inclusion of 12 months data points before reclassification provided sufficient baseline data to estimate both level and slope changes, as recommended in methodological guidance for interrupted time-series designs [24,25,32]. This approach is consistent with previous interrupted time-series analyses evaluating policy impacts on medicine use [33–36]. Segmented regression was employed to estimate level and trend changes associated with gabapentinoid reclassification and COVID-19 lockdowns. This approach enables straightforward estimation and interpretation of policy effects at defined time points and has been successfully used in previous studies utilizing similar national prescribing datasets [33–36]. Diagnostic checks (Durbin – Watson statistics and autocorrelation plots) showed no significant autocorrelation, supporting the suitability of this method over ARIMA-based models, which are less intuitive for interpreting policy effects when the autocorrelation structure is weak or non-significant.

3. Results

3.1. Overall utilization trend of gabapentinoids in Scotland and NI

Overall, there were a total of 2,076 items dispensed per 1,000 inhabitants in Scotland and 2,050 items dispensed per 1,000 inhabitants in NI during the study period. The DID in Scotland over the study period was 52,501, with 58% (30,451 TID) pregabalin and 42% (22,050 TID) gabapentin, whereas in NI, the DID was 43,185, with 67% (28,933 DID) pregabalin and 33% (14,252 DID) gabapentin, indicating generally higher overall utilization in Scotland.

In Scotland, there was a 50% split between items dispensed for pregabalin and gabapentin, whereas in NI, 57% (1,176 TID) of dispensed items were pregabalin, suggesting more utilization of pregabalin. As the TID plot shows (Figure 1), total gabapentinoid utilization was initially higher in NI than in Scotland, although Scotland reached the NI level and

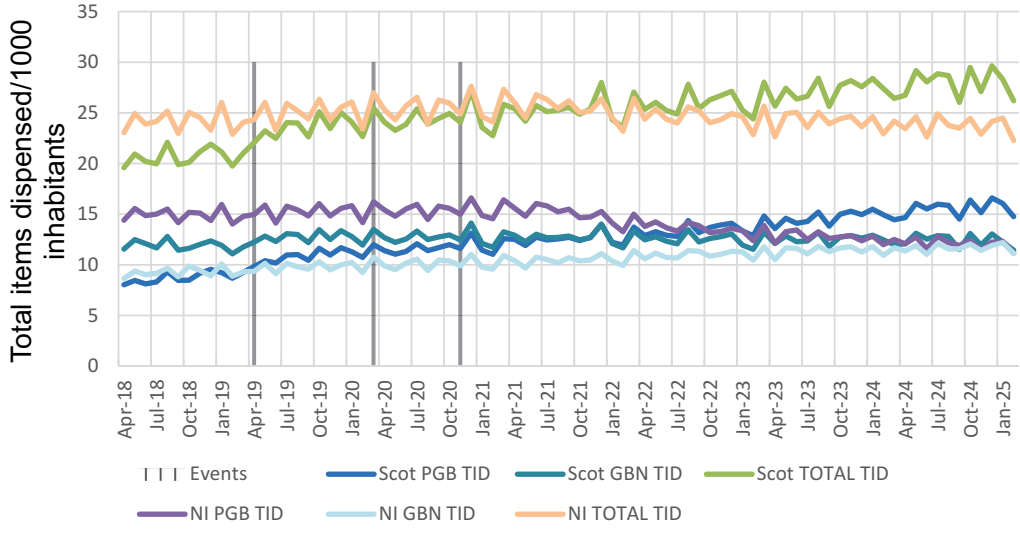

Figure 1. Total items dispensed per 1,000 inhabitants for Scotland and Northern Ireland (ni) from April 2018 to February 2025, with the three events labeled starting with gabapentinoids reclassification in 2019, first COVID-19 lockdown in March 2020 and second COVID-19 lockdown in November 2020. PGB = pregabalin GBN = gabapentin.

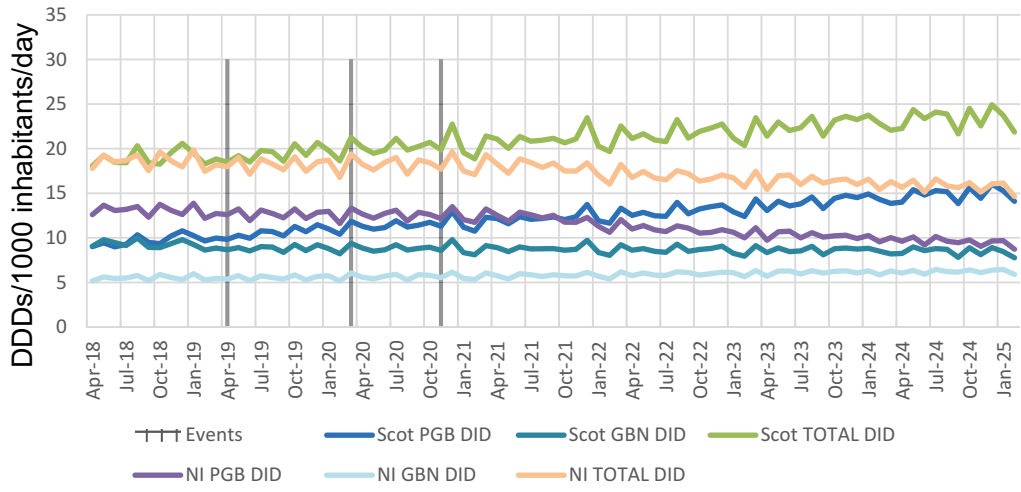

Figure 2. DDDs per 1000 inhabitants/day for Scotland and Northern Ireland (ni) from April 2018 to February 2025, with the three events labeled starting with gabapentinoids reclassification in 2019, first COVID-19 lockdown in March 2020 and second COVID-19 lockdown in November 2020. ddd = defined daily dose PGB = pregabalin GBN = gabapentin.

ultimately surpassed it in April 2022. For DIDs (Figure 2), total gabapentinoid usage started at a similar point in both countries in April 2018, then diverged, with NI declining at around July 2019. It seems that pregabalin TID in Scotland is the driving factor, as it started below eight items dispensed per 1,000 inhabitants per month in April 2018 and surged to 15 in February 2025.

Overall, Scotland experienced a 34% increase in total TID (6.61 items per 1,000 inhabitants), whereas NI showed 3% decline (−0.78 items per 1,000 inhabitants). For DID, Scotland's total increased by 21%, whereas NI's declined by 18% (Table 1).

In terms of monthly changes overtime, in Scotland, the average monthly change in total gabapentinoids TID was 0.092, a significant increase (95% CI: 0.081–0.103; p-value: < 0.05) (Table 1). The increase in Scotland's total gabapentinoids was also evident for both pregabalin and gabapentin. This was particularly notable for pregabalin, where TID increased by 84% (6.73 items) and DID by 56% (5.09 DDDs), both with highly significant monthly growth rates (TID: 0.089; DID: 0.072; p-value: < 0.05). Meanwhile, in NI, there was a decline in pregabalin utilization, with TID decreasing by 23% and DID by 31% (Table 1). Gabapentin use remained relatively stable in Scotland, with a non-significant increase in TID (0.003; 95% CI: −0.003–0.008; p-value = 0.33) (Table 1). In contrast, gabapentin in NI showed a significant increase in TID by 29% and DID by 14%, partially offsetting the decline in pregabalin.

NI's TID was initially higher but remained flat, showing no increase between April 2018 and February 2025, whereas Scotland's TID showed an upward trend, surpassing that of NI by the end of the study period, particularly for pregabalin (Figures 1 and 2),

3.2. Impact of gabapentinoids reclassification and COVID-19 lockdowns

Following the segmented regression analysis, all beta-coefficient results were non-significant, except for the baseline slope (β1) for Scotland TID pregabalin (0.102, 95% CI: 0.006–0.198; p-value = 0.038) and DID pregabalin (0.101, 95% CI: 0.004–0.199; p-value = 0.042) (Table 2). This indicates

Table 1. Initial value, final value, absolute, relative and average monthly changes for gabapentinoids in terms of total items dispensed/1,000 inhabitants and defined daily dose/1,000 inhabitants/day during the study period (April 2018–February 2025).

	Initial value (April 2018)	Final value (Feb. 2025)	Absolute change	Relative change	Average monthly change (AMC) (95% CI: *p*-value)
Scotland					
TID					
Total Gabapentinoids	19.59	26.20	6.61	34%	0.092 (0.081–0.103: *p*-value < 0.05)
Pregabalin	8.03	14.76	6.73	84%	0.089 (0.083–0.095: *p*-value < 0.05)
Gabapentin	11.56	11.44	−0.12	−1%	0.003 (−0.003–0.008: *p*-value = 0.33)
DID					
Total Gabapentinoids	18.07	21.87	3.80	21%	0.063 (0.054–0.071: *p*-value < 0.05)
Pregabalin	9.01	14.10	5.09	56%	0.072 (0.066–0.077: *p*-value < 0.05)
Gabapentin	9.06	7.77	−1.29	−14%	−0.009 (−0.005 to −0.012: *p*-value < 0.05)
NI					
TID					
Total Gabapentinoids	23.06	22.28	−0.78	−3%	−0.019 (−0.034 to −0.004: *p*-value < 0.05)
Pregabalin	14.41	11.15	−3.26	−23%	−0.046 (−0.053 to −0.038: *p*-value < 0.05)
Gabapentin	8.65	11.13	2.48	29%	0.027 (0.016–0.038: *p*-value < 0.05)
DID					
Total Gabapentinoids	17.79	14.64	−3.15	−18%	−0.042 (−0.051 to −0.033: *p*-value < 0.05)
Pregabalin	12.61	8.73	−3.88	−31%	−0.051 (−0.056 to −0.046: *p*-value < 0.05)
Gabapentin	5.18	5.91	0.73	14%	0.009 (0.002 – 0.015: *p*-value < 0.05)

Abbreviations: TID = total items dispensed/1,000 inhabitants; DID = defined daily doses/1,000 inhabitants/day.

Table 2. Segmented regression analysis of total items dispensed per 1,000 inhabitants and defined daily dose per 1,000 inhabitants per day during the study period April 2018–February 2025.

	Baseline trend (β_1)	Change immediately after the reclassification (β_2)	Time trend after gabapentinoids reclassification (β_3)	Change immediately after first COVID-19 lockdown (β_4)	Time trend after first COVID-19 lockdown (β_5)	Change immediately after second COVID-19 lockdown (β_6)	Time trend after second COVID-19 lockdown (β_7)
Scotland							
TID							
Total Gabapentinoids	0.064 (−0.126–0.254: *p*-value = 0.504)	1.707 (−0.184–3.599: *p*-value = 0.076)	0.062 (−0.225–0.350: *p*-value = 0.666)	0.178 (−1.928–2.285: *p*-value = 0.866)	−0.109 (−0.506–0.288: *p*-value = 0.587)	−0.027 (−1.570–1.516: *p*-value = 0.972)	0.057 (−0.282–0.396: *p*-value = 0.739)
Pregabalin	0.102 (0.006–0.198: *p*-value = 0.038)	0.790 (−0.168–1.748: *p*-value = 0.104)	0.017 (−0.129–0.162: *p*-value = 0.820)	0.014 (−1.053–1.081: *p*-value = 0.979)	−0.079 (−0.280–0.122: *p*-value = 0.435)	−0.075 (−0.856–0.707: *p*-value = 0.850)	0.043 (−0.128–0.215: *p*-value = 0.618)
Gabapentin	−0.038 (−0.133–0.057: *p*-value = 0.432)	0.917 (−0.030–1.863: *p*-value = 0.057)	0.046 (−0.098–0.190: *p*-value = 0.528)	0.164 (−0.890–1.219: *p*-value = 0.757)	−0.030 (−0.228–0.169: *p*-value = 0.768)	0.048 (−0.725–0.820: *p*-value = 0.903)	0.014 (−0.156–0.183: *p*-value = 0.872)
DID							
Total Gabapentinoids	0.057 (−0.107–0.221: *p*-value = 0.490)	−0.440 (−2.074–1.194: *p*-value = 0.593)	0.024 (−0.224–0.272: *p*-value = 0.848)	0.588 (−1.232–2.407: *p*-value = 0.522)	−0.092 (−0.435–0.252: *p*-value = 0.597)	0.015 (−1.318–1.348: *p*-value = 0.982)	0.076 (−0.217–0.369: *p*-value = 0.606)
Pregabalin	0.101 (0.004–0.199: *p*-value = 0.042)	−0.243 (−1.212–0.725: *p*-value = 0.618)	−0.007 (−0.154–0.140: *p*-value = 0.924)	0.303 (−0.775–1.381: *p*-value = 0.577)	−0.078 (−0.282–0.125: *p*-value = 0.445)	−0.055 (−0.845–0.735: *p*-value = 0.890)	0.058 (−0.116–0.231: *p*-value = 0.511)
Gabapentin	−0.044 (−0.112–0.024: *p*-value = 0.202)	−0.197 (−0.875–0.482: *p*-value = 0.565)	0.031 (−0.072–0.134: *p*-value = 0.550)	0.285 (−0.471–1.040: *p*-value = 0.455)	−0.013 (−0.156–0.129: *p*-value = 0.854)	0.070 (−0.484–0.623: *p*-value = 0.802)	0.018 (−0.103–0.140: *p*-value = 0.763)
NI							
TID							
Total Gabapentinoids	0.015 (−0.254–0.283: *p*-value = 0.914)	0.733 (−1.937–3.402: *p*-value = 0.586)	−0.013 (−0.418–0.393: *p*-value = 0.951)	0.765 (−2.208–3.738: *p*-value = 0.610)	−0.034 (−0.595–0.526: *p*-value = 0.903)	0.546 (−1.632–2.724: *p*-value = 0.619)	−0.029 (−0.507–0.449: *p*-value = 0.905)
Pregabalin	−0.019 (−0.123–0.085: *p*-value = 0.713)	0.478 (−0.557–1.512: *p*-value = 0.361)	0.008 (−0.149–0.166: *p*-value = 0.916)	0.472 (−0.681–1.624: *p*-value = 0.417)	−0.027 (−0.244–0.191: *p*-value = 0.808)	0.384 (−0.461–1.228: *p*-value = 0.368)	−0.044 (−0.229–0.141: *p*-value = 0.638)
Gabapentin	0.034 (−0.180–0.248: *p*-value = 0.753)	0.255 (−1.872–2.382: *p*-value = 0.812)	−0.021 (−0.344–0.302: *p*-value = 0.898)	0.293 (−2.077–2.662: *p*-value = 0.806)	−0.008 (−0.454–0.439: *p*-value = 0.972)	0.163 (−1.573–1.898: *p*-value = 0.853)	0.015 (−0.366–0.396: *p*-value = 0.937)
DID							
Total Gabapentinoids	−0.019 (−0.143–0.105: *p*-value = 0.766)	−0.020 (−1.253–1.213: *p*-value = 0.974)	−0.029 (−0.216–0.159: *p*-value = 0.761)	0.757 (−0.616–2.131: *p*-value = 0.276)	−0.015 (−0.274–0.244: *p*-value = 0.909)	0.200 (−0.807–1.206: *p*-value = 0.694)	0.005 (−0.216–0.226: *p*-value = 0.962)
Pregabalin	−0.030 (−0.114–0.055: *p*-value = 0.489)	−0.007 (−0.848–0.834: *p*-value = 0.987)	−0.014 (−0.141–0.114: *p*-value = 0.834)	0.532 (−0.405–1.468: *p*-value = 0.262)	−0.012 (−0.189–0.164: *p*-value = 0.889)	0.210 (−0.476–0.897: *p*-value = 0.544)	−0.014 (−0.165–0.137: *p*-value = 0.855)
Gabapentin	0.011 (−0.031–0.053: *p*-value = 0.605)	−0.013 (−0.430–0.403: *p*-value = 0.949)	−0.015 (−0.078–0.048: *p*-value = 0.635)	0.226 (−0.238–0.690: *p*-value = 0.336)	−0.002 (−0.090–0.085: *p*-value = 0.955)	−0.011 (−0.351–0.329: *p*-value = 0.950)	0.019 (−0.055–0.094: *p*-value = 0.610)

Abbreviations: TID = total items dispensed/1,000 inhabitants; DID = defined daily dose/1,000 inhabitants/day.

a significant increase in pregabalin monthly baseline TID and DID in Scotland (Table 2).

For Scotland TID, change immediately after reclassification (β2) was comparatively higher than the other coefficients. This represents the effect immediately after the reclassification of gabapentinoids and was high for total gabapentinoids, pregabalin, and gabapentin, coming close to being statistically significant. This suggests that utilization increased following the reclassification (Table 2), albeit statistically non-significantly. In terms of DID, pregabalin baseline trend was significantly positive, as noted above, change immediately after reclassification was negative across all medicines and change immediately after first lockdown (β4) was high across all medicines, indicating a trend change following the first COVID-19 lockdown (Table 2).

For NI, TID results for change immediately after first lockdown (β4) and change immediately after second lockdown (β6) were high for all medicines (Table 2), indicating that utilization increased after each COVID-19 lockdown, although these results were not statistically significant. While not significant, the highest DID results were also seen for change immediately after first lockdown (Table 2). Both Scotland and NI showed elevated DID change immediately after first lockdown results, suggesting an upward trend in DDDs intake following the first COVID-19 lockdown, although this was not significant.

Comparing the two countries, Scotland had a significant increase in the baseline trend for pregabalin metrics. There was also variation in the regression direction for the time trend following reclassification (β3) (Table 2). A similar variation was observed for β6, the level change immediately after the second COVID-19 lockdown. Time trend after second lockdown (β7), for Scotland exhibited a consistently positive slope, reflecting the time trend after the second COVID-19 lockdown. In contrast, NI showed a negative slope for pregabalin metrics for time trend after second lockdown, which reversed the total gabapentinoids TID slope to −0.029 (95% CI: −0.507–0.449; p-value = 0.905) (Table 2). The segmented regression models demonstrated a close fit to the observed data, with minimal residual variation and no systematic deviation, supporting the adequacy of the model specification.

3.3. Gabapentinoid-related deaths compared to utilization

After calculating the Pearson coefficient between gabapentinoid-related deaths and utilization figures, a positive correlation was found, but it was not statistically significant, where in Scotland TID coefficient was 0.119 (95% CI – 0.345–0.582: p-value = 0.517) and DID was 0.073 (95% CI – 0.809–0.955: p-value = 0.830), while for NI TID was 0.478 (95% CI – 0.289–-1.244: p-value = 0.158) and DID 0.098 (95% CI – 0.601–0.797: p-value = 0.717). This indicates that, statistically, an increase in utilization did not correlate with an increase in mortality. It might be disadvantageous to fully depend on p-values, which were no less than 0.1 in any regression. However, as shown in Figures 3 and 4, which depict total gabapentinoids TIDs and gabapentinoid-related deaths in each country, annual mortalities were variable and did not form a consistent trend in either country. Meanwhile, annual TID figures in Scotland appeared to increase, whereas in NI, there was a peak followed by a decline after 2022.

4. Discussion

4.1. Key findings

Findings of this study suggest that overall utilization of gabapentinoids in Scotland was higher than in NI, and that gabapentinoids use in Scotland significantly increased over the study period (TID: 34% DID: 21%; p-value: < 0.05), whereas it significantly decreased in NI (TID: −3% DID: −18%; p-value: < 0.05). The difference between the two countries may be due to differing national guidelines, where alongside National Institute for Health and Care Excellence (NICE), Scotland also uses Scottish Intercollegiate Guidelines Network (SIGN), whereas NI uses Northern Ireland Formulary (NIF) guidelines [37,38]. Even though all are within the UK, different guidelines can recommend gabapentinoids for different indications and different lines of treatment. For example, since July 2021, pregabalin is no longer indicated for new patients with neuropathic pain in the NIF [39]. This change is reflected in the plots (Figures 1 and 2), where NI pregabalin metrics decreased toward the end of 2021. Neuropathic pain is one of the main indications for pregabalin and is included as a first-line treatment in NICE guidelines [40]. The difference between the two countries may be due not only to differing national guidelines but also to variations in prescribing policies. While NHS prescriptions are free for all residents in both Scotland and NI, facilitating similar reimbursement conditions, prescribing access differs between the two countries. Gabapentinoids are listed for nurse independent prescribers in Scotland but not in NI [41,42]. which may partly account for the higher utilization observed in Scotland.

Another key finding is that in Scotland, gabapentin DID significantly decreased, whereas TID increased (Table 1). However, the TID increase was non-significant, and the relative change was negative. The contrast between TID and DID may suggest that lower doses were more commonly used over time. Furthermore, the reclassification and the COVID-19 lockdowns did not result in any significant change in utilization patterns. One of the likely determinants of this result may be that reclassification from Schedule 4 to Schedule 3 did not heavily restrict access to gabapentinoids [14]. Even without repeat prescriptions or emergency supplies, patients could still obtain gabapentinoids on monthly basis.

Moreover, the analysis did not identify a statistically significant correlation between gabapentinoid utilization and related mortality in either country. While p-values were consistently high (> 0.1), this should not be interpreted as definitive evidence of no association but rather as an indication of uncertainty in the available data. The absence of a clear trend in Figures 3 and 4 and the wide confidence intervals in the Pearson coefficients together suggest that, within the limitations of aggregated national data, no consistent relationship between utilization and mortality could be demonstrated. It is notable that after 2019, gabapentinoid-related deaths per 1 million inhabitants in Scotland were all above 80, except in

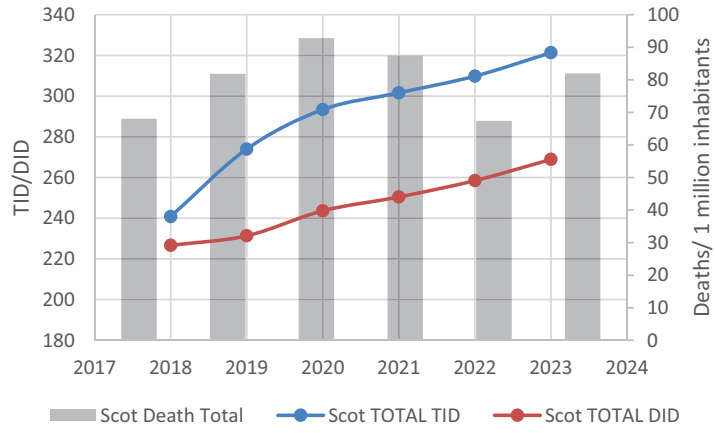

Figure 3. Gabapentinoid-related deaths per 1 million inhabitants in Scotland compared to utilization from April 2018 to February 2025. tid = total items dispensed/1,000 inhabitants; did = defined daily dose/1,000 inhabitants/day.

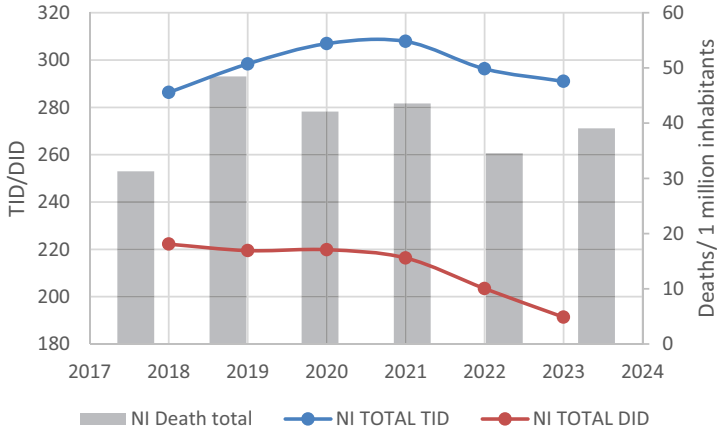

Figure 4. Gabapentinoid-related deaths per 1 million inhabitants in Northern Ireland (ni) compared to utilization from April 2018 to February 2025. tid = total items dispensed/1,000 inhabitants; did = defined daily dose/1,000 inhabitants/day.

2022, where the figure was 67 (Figure 3). All drug-related deaths in Scotland were also lower in 2022 than in other years, making pregabalin and gabapentin related mortalities no different from pre-reclassification and pre-COVID-19 in 2018 and in earlier studies [6].

4.2. Findings in the context of published literature

Pregabalin was consistently the driving factor behind the direction of change in each country. The findings were concordant with a previous study, which covered the period 2010–2019 [6]. However, the absence of a sustained long-term impact of the reclassification in our study contrasts with an earlier study that reported a short-term reduction in utilization in the UK following the policy change [8]. This discrepancy suggests that while the reclassification may have had an initial effect on prescribing behavior, its influence was not maintained over time, indicating potential adaptation within clinical practice or prescribing systems to circumvent the restrictions. When compared with the reclassification of other medicines, such as tramadol – which was reclassified as a Schedule 3 controlled drug in 2014 [43], studies indicate that tramadol utilization declined significantly following reclassification [44]. In contrast, gabapentinoid reclassification did not demonstrate a comparable long-term reduction in use. One possible explanation, beyond the additional regulatory restrictions associated with Schedule 3 classification, is that tramadol is predominantly prescribed for post-operative pain, a short-term indication for which alternative opioids are readily available. On the other hand, gabapentinoids are indicated for longer-term and more diverse conditions, including neuropathic pain, epilepsy, and generalized anxiety disorder, which may limit substitution and contribute to their continued utilization. While international awareness of the opioid crisis, particularly in the United States, may have indirectly influenced prescriber caution in the UK, there is currently no empirical evidence to confirm a measurable impact on national gabapentinoid utilization trends.

The absence of a measurable impact of COVID-19 lockdowns on gabapentinoid utilization in Scotland and NI may be explained by the resilience of primary care prescribing and dispensing systems, coupled with the methodological limitations of aggregated data. Throughout the COVID19 lockdowns, community pharmacies and general practices in Scotland were formally designated as essential services and remained operational to ensure continuity in medicines supply; notably, a nationally commissioned, timelimited NHS Medicines Delivery Service – coordinated via the Community

Pharmacy Network – was established in January 2021 to facilitate home delivery of medications to those shielding or self-isolating [45]. Such adaptations likely enabled patients on long-term gabapentinoid therapy to maintain uninterrupted access. In line with this, several UK-based prescribing studies across diverse therapeutic areas documented transient surges in dispensing at the outset of the COVID19 pandemic, followed shortly thereafter by a return to baseline trends, indicating no sustained interruption in long-term medication utilization. For instance, it was observed that total monthly prescriptions across all British National Formulary categories peaked in March 2020 – the highest in five years – before resuming prior trajectories [46].

Our findings can also be considered in the context of emerging international data on gabapentinoid regulation and utilization. In France, recent policy interventions appear to have produced more pronounced effects than those observed in the UK. A study reported a significant and sustained reduction in pregabalin dispensations following the 2021 regulatory restrictions that required secure prescription pads, suggesting that stricter national controls can rapidly influence prescribing behavior [47]. Similarly, another study observed a decline in new pregabalin initiations but a concurrent rise in gabapentin use between 2017 and 2021, reflecting potential therapeutic substitution [48]. In contrast, our analysis found no immediate or sustained changes in utilization following the UK reclassification or during the COVID-19 lockdowns, implying that existing regulatory mechanisms – such as Schedule 3 classification – may have had more limited behavioral impact. These international differences likely reflect variations in regulatory stringency, prescriber oversight, and the timing of implementation across jurisdictions [47,48].

Importantly, the use of aggregated prescribing data, which does not differentiate between incident and prevalent users, may have masked differential impacts. While initiation of new medicines may have declined, maintenance prescribing for prevalent users was largely preserved. For example, large-scale analyses of cardiovascular medicines in the UK demonstrated marked reductions in treatment initiation during lockdown, despite overall dispensing remaining stable [49]. This dynamic could similarly apply to gabapentinoids, where stable aggregate utilization may obscure reductions in new prescribing. Finally, because gabapentinoids were reclassified as Schedule 3 controlled drugs in 2019, they were not eligible for emergency supply at community pharmacies, unlike some other medicines. Consequently, prescribers may have prioritized timely repeat prescribing to avoid treatment interruptions, reinforcing continuity and limiting observable disruption in dispensing patterns.

4.3. Strengths and limitations

Various points ensure that this study contributes to the current knowledge on this topic, including that it uses population data covering the entire population. More than one metric was used to assess utilization, with each compensating for disadvantages in the others. In some cases, DID can be a more accurate reflection of utilization than TID because the latter only represents the number of items and not the quantity dispensed. While DID is the preferred standardized metric, TID was retained to offer complementary insight into prescribing frequency and dispensing practices. Nonetheless, interpretation should be made cautiously given the potential variation in pack sizes and strengths. Drug-related mortality was studied and linked to utilization to measure long-term impacts and compare utilization patterns before and after the interventions. Furthermore, the study covered a relatively long period of nearly seven years, allowing for a comprehensive assessment of monthly prescribing patterns and overall utilization trends. The use of segmented regression enabled evaluation of the long-term impact of both the reclassification and the COVID-19 pandemic, representing the gold-standard approach for assessing changes in utilization over time.

On the other hand, one of the key limitations of this study is its reliance on aggregated rather than patient-level data, which restricts the ability to explore individual clinical or demographic factors that may influence prescribing, such as age, comorbidities, concomitant medications, or socioeconomic status. This limitation also precludes examination of appropriateness of prescribing, dose escalation, treatment duration, or potential misuse, which are important considerations in evaluating the real-world impact of gabapentinoid use. However, population studies can serve as a first step to generate hypotheses for patient-level research. The analysis was limited by the small number of available data points for drug-related deaths, with only six annual observations available across the study period, which constrained the study's statistical power and may have increased uncertainty around correlation estimates. Nevertheless, these data represent the only available national mortality figures spanning both the reclassification and pandemic periods, providing important preliminary insights pending future analyses with more granular data. Furthermore, national definitions of 'drug-related deaths' in Scotland and NI record fatalities only when gabapentinoids are detected in postmortem toxicology or explicitly listed on death certificates. This may have led to underestimation of the true burden, particularly in cases where gabapentinoids contributed to harm but were not identified or reported. Moreover, we were unable to distinguish between new and ongoing gabapentinoid users, which may have obscured any pandemic-related changes in prescribing behavior. Similar findings have been observed in other therapeutic areas, where the impact of COVID-19 was evident only when analyses focused on patients newly starting antihypertensive therapy [49]. A similar analytical approach could be adopted in future research to examine new initiations of gabapentinoid prescriptions as a comparative indicator. Finally, we did not know the indications for the studied prescriptions, and some conditions may have a higher risk of misuse than others. However, this could also be seen as a strength, since including all prescriptions offers a comprehensive picture of overall utilization.

5. Conclusion

In conclusion, gabapentinoid utilization increased overall during the study period, particularly in Scotland, whereas a modest decline was observed in NI. These divergent trends appear to be driven by differences in national formularies and prescribing

policies rather than by the 2019 reclassification of gabapentinoids or the COVID-19 national lockdowns, neither of which produced a measurable impact on utilization patterns. Furthermore, no significant correlation was identified between gabapentinoid use and gabapentinoid-related mortality, suggesting that rising prescribing levels alone may not directly translate into increased mortality risk at the population level.

Together, these findings highlight the need for harmonized national guidance and closer monitoring of controlled drug prescribing across UK jurisdictions. Future research should utilize patient-level data to clarify clinical characteristics, treatment indications, and potential misuse patterns associated with gabapentinoids, and to investigate the complex relationship between utilization, dependence, and mortality. Such evidence will be essential to inform balanced policy measures and optimize the safe and appropriate use of gabapentinoids within clinical practice.

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Author contributions

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Ethics statements

No ethical approval or participation consent was required for this paper in accordance with national legislation and institutional requirements.

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