Use of gabapentinoid treatment and the risk of self-harm: population based self-controlled case series study

Andrew S C Yuen,[1,2] Boqing Chen,[1,2] Adrienne Y L Chan,[3,4] Joseph F Hayes,[5,6] David P J Osborn,[5,6] Frank M C Besag,[1,7,8] Wallis C Y Lau,[1,2,4,9] Ian C K Wong,[1,4,9,11] Li Wei,[1,2] Kenneth K C Man[1,2,4,9]

For numbered affiliations see end of the article

Correspondence to: K K C Man kenneth.man@ucl.ac.uk (@KennethKCMan on x.com; ORCID 0000-0001-8645-1942)

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ABSTRACT

OBJECTIVE

To estimate the effect of gabapentinoid treatment on self-harm.

DESIGN

A population based self-controlled case series study.

SETTING

UK Clinical Practice Research Datalink Aurum database linked to the Hospital Episode Statistics and Office for National Statistics databases.

PARTICIPANTS

10 002 adults (aged ≥18 years), with gabapentinoid prescriptions, who had an incident event of self-harm between 1 January 2000 and 31 December 2020. Individual censoring occurred on the date of epilepsy, substance misuse, or cancer diagnosis.

MAIN OUTCOME MEASURES

Crude incidence rates of self-harm in different risk periods: 90 days before gabapentinoid treatment, gabapentinoid treatment period, 14 days after treatment periods, and reference periods were calculated. Conditional Poisson regression derived the incidence rate ratio and 95% confidence intervals (CIs) to evaluate the risk of self-harm in different risk periods, compared with reference period for each individual.

RESULTS

1 503 597 individuals received gabapentinoid prescriptions and 10 002 individuals were included in the analysis. The incidence rate of self-harm per 100 person years was 16.79 (95% CI 16.65 to 16.92) in the 90 days before treatment period, 9.66 (9.62 to 9.70) in the treatment period, 29.60 (29.09 to 30.11) in the 14 days after treatment period, and 6.75 (6.74 to 6.77) in the reference period. The results yielded an increased risk of self-harm during the 90 day period before treatment, with an adjusted incidence rate ratio of 1.69 (95% CI 1.55 to 1.85). The spline based analysis showed that the risk of self-harm declined gradually around the time of treatment initiation and returned to reference level during the treatment period (adjusted incidence rate ratio 1.06 (0.98 to 1.13)). Adjusted incidence rate ratio for self-harm increased within 14 days after treatment cessation (3.02 (2.53 to 3.60)). The findings remained consistent throughout a series of subgroups and sensitivity analyses.

CONCLUSIONS

The association between gabapentinoids and risk of self-harm seems to be multifaceted: an elevated risk of self-harm is present before initiation of gabapentinoid treatment, which persists during the initial phase of the treatment period, and rises again shortly after treatment discontinuation. These findings do not support a direct effect of gabapentinoid treatment on self-harm but underscore the necessity for close patient monitoring of self-harm throughout the gabapentinoid treatment journey.

WHAT IS ALREADY KNOWN ON THIS TOPIC

The risk of self-harm with gabapentinoid use and was unclear, with previous studies yielding conflicting results and having limitations such as residual confounders

Previous studies did not examine the risks immediately before starting or after stopping gabapentinoid treatment, despite many of the drug indications being associated with self-harm

A comprehensive investigation was needed to investigate this association thoroughly, to evaluate self-harm risks in periods before, during, and after gabapentinoid treatment

WHAT THIS STUDY ADDS

Risk of self-harm is increased before treatment (1.69 (95% confidence interval 1.55 to 1.85)), persists during the initial treatment period, and rises again shortly after discontinuation

Healthcare providers should closely monitor patients for self-harm not only during gabapentinoid treatment but also before initiation and after discontinuation, considering underlying conditions that may contribute to the risk

Introduction

Gabapentinoids (including gabapentin and pregabalin) were originally developed as antiseizure medications,[1] with gabapentin first being marketed in 1993.[2] With their inhibitory properties on the central nervous system,[3] gabapentinoids are licensed for the treatment of epilepsy, neuropathic pain, and generalised anxiety disorder in the UK.[4-7] However, more than 50% of these gabapentinoid prescriptions are for unlicensed conditions,[8] which have limited evidence supporting their use.[2 9] Recorded indications for gabapentinoids also include restless legs syndrome, complications of multiple sclerosis, chronic pain, musculoskeletal pain, postoperative pain, insomnia, and bipolar disorder.[4-7]

Opioids and benzodiazepines, which share indications with gabapentinoids, such as neuropathic pain, chronic pain, or generalised anxiety disorder, show mixed or declining prescription trends worldwide[10 11]; conversely, gabapentinoid consumption was noted to increase fourfold from 2008 to 2018.[12] The increase in consumption has also been documented in various national studies,[13-17] sparking concerns among regulatory bodies and the media regarding the potential for dependency,

misuse, and psychological adverse effects associated with gabapentinoids.[18-20] In response, additional labelling requirements and rescheduling as controlled substances were introduced in different countries across the globe.[21-24] For instance, the UK Medicines and Healthcare products Regulatory Agency have reclassified gabapentinoids to Schedule 3 controlled drugs in 2019.[21]

In 2008, the US Food and Drug Administration, based on previous clinical trials of different types of antiseizure medications, issued a report indicating an increased risk of suicidality among patients who took antiseizure medications, including gabapentinoids.[25] Recent observational studies have found conflicting results related to the association between gabapentinoids and the risk of self-harm attempts or behaviours.[26-31] In addition, these studies either compared gabapentinoids with other antiseizure medications, were limited to a specific group of patients, or were subject to residual confounders. The risks immediately before starting and after stopping gabapentinoid treatment were also never explored in any of the studies; although, many of its indications are associated with suicidal ideation.[23 32-35] With the rapid increase in gabapentinoids consumption in recent years, a better understanding of the safety of gabapentinoids is needed. To address the concerns, we conducted a self-controlled case series analysis of a population based cohort and aimed to estimate the effect of gabapentinoid treatment on self-harm.

Methods

Data sources

We used data from the UK Clinical Practice Research Datalink Aurum linked to the Hospital Episode Statistics and Office for National Statistics databases from England. This database encompasses data for approximately 40 million patients across nearly 1500 general practices[36] and is representative of the general population of England for age, sex, and ethnic groups.[37] Medical diagnoses and procedures are documented using the Read code and SNOMED-CT classification systems, while prescription information is captured through a coded drug dictionary derived from the British National Formulary.[38] The reliability of the data recorded in the Clinical Practice Research Datalink has been shown by prior research.[39 40]

The Hospital Episode Statistics database contains hospital admission records of patients who have received care from National Health Services hospitals in England.[41] Diagnoses in the Hospital Episode Statistics are recorded using the International Classification of Diseases, 10th revision (ICD-10) classification.[41] The Office for National Statistics database is a vital statistics database that we used to accurately identify patients who died during follow-up and their cause of death.

Self-controlled case series design

We used the self-controlled case series design to investigate the association between gabapentinoid use and self-harm.[42 43] It has previously been used to investigate the safety effects of different medications in various health conditions.[44-48] The self-controlled case series design includes patients who have the outcome and treatment of interest within a prespecified period. Included patients serve as their own controls.[42] The major advantage of this design is that all time constant confounders are removed, whether measured or unmeasured, which vary between individuals. Incidence rate ratios were derived by comparing the incidence rate of events during treatment periods with non-treatment periods. Furthermore, we adjusted for time varying factors, including age in one year bands, season (in three month intervals starting from December to February) and concomitant use of opioids and psychotropic medications, which potentially affect gabapentinoid use and the risk of self-harm.[49-51]

Case identification

We identified adults (aged ≥18 years) who received at least one prescription of gabapentinoids (supplementary table 1) and had their first Hospital Episode Statistics record of self-harm dated during the study period (1 January 2000 to 31 December 2020). Since a previous study has reported inaccuracy of self-harm recording within primary care records,[52] the study outcome was defined as incident self-harm identified in records of hospital admission through the Hospital Episode Statistics database with ICD-10 diagnostic codes X60-X84 and Y10-Y34, excluding Y33.9 (supplementary table 2).[53]

Individual observation periods commenced on 1 January 2000; the date the individual registered with the Clinical Practice Research Datalink contributing practice; or the 18th birthday of the patient (whichever was later). The period ended either on 31 December 2020; the date of registered death; the date that the individual's registration at the practice ended; or at diagnosis date of epilepsy, substance misuse, or cancer (whichever was earliest). Patients with these conditions occurring before the start of the observational period were excluded or censored on date of diagnosis if occurring after, as they have different drug usage patterns and risk of self-harm.[54-56] Any individuals with missing information for year of birth or sex were excluded. Individuals where the event occurred on the first day of gabapentinoid treatment were also excluded to avoid outcome misclassification because such events might be attributed to factors before treatment and could be incorrectly assigned to the treatment period. Supplementary figure 1 illustrates the selection of the study population.

Exposures and outcomes

We identified all gabapentinoid prescriptions and incident self-harm events for each individual. We did not exclude prescriptions based on gabapentinoid formulation or strength. We defined treatment periods as the time individuals received gabapentinoids and these were calculated by adding the duration to the start date of prescriptions. We first used the recorded

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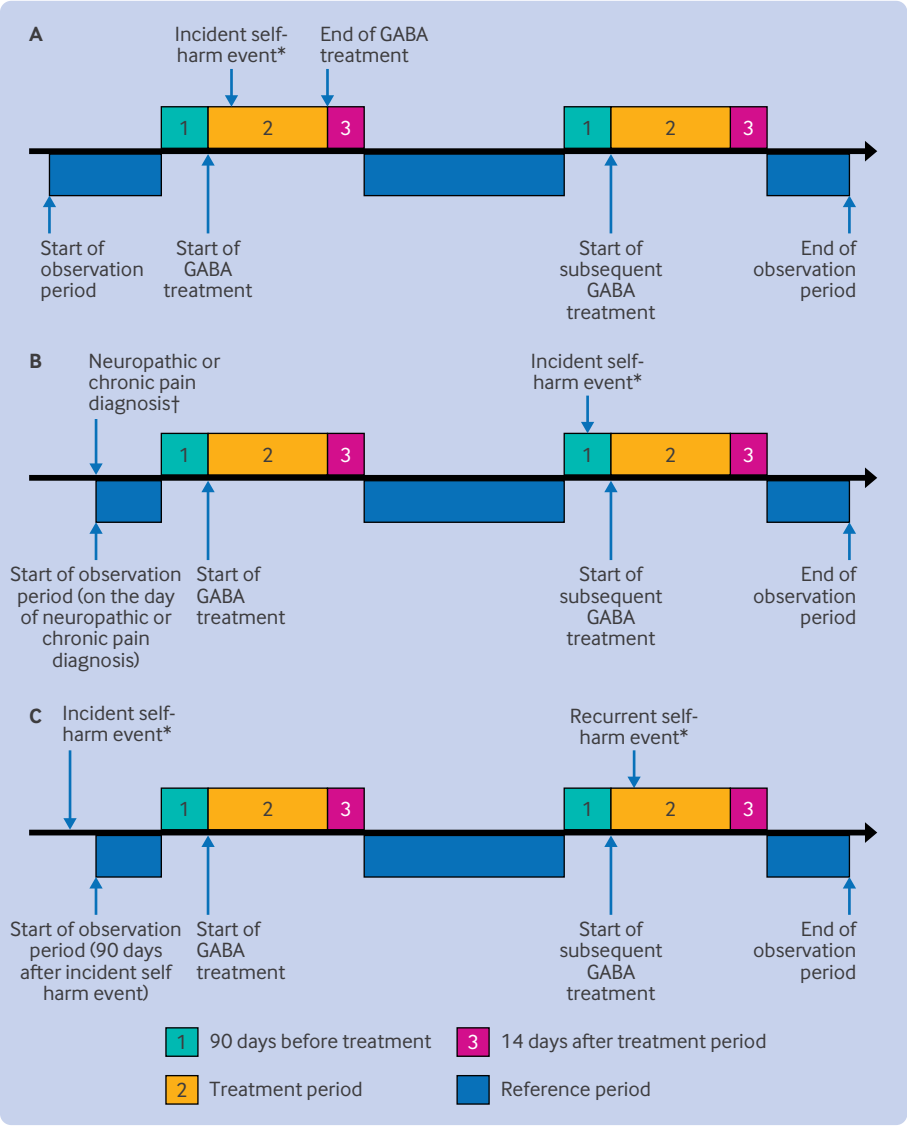

Fig 1 | Self-controlled case-series study design. (A) Illustration of the study design and timeline for a single hypothetical participant. (B) Observation starts at neuropathic or chronic pain diagnosis. (C) Recurrent self-harm. *Event can happen at any time throughout the observation period. †Neuropathic or chronic pain diagnosis can happen at any time throughout the observation period. GABA=gabapentinoids

prescription duration if it was available. The quantity and daily doses prescribed were then used to determine the duration of treatment if prescription duration was not available. More than 90% of the gabapentinoid prescriptions had either duration or quantity and daily doses recorded. Where this information was missing, we imputed the median prescription duration of 28 days. Gabapentinoid prescriptions that were less than or equal to 90 days apart were treated as a continuous treatment period. In this study, we divided patient time into four discrete windows: 90 days before gabapentinoid treatment; treatment periods; 14 days after gabapentinoid treatment periods; and reference periods (the person time that falls outside of the three other categories) (figure 1). A risk window of 90 days before treatment was added to account for the possibility that the episode of self-harm may affect the likelihood of gabapentinoid treatment, which in turn may introduce bias into the risk estimate during treatment.[42] A period of 14 days after treatment was added to explore the risk of self-harm after gabapentinoid treatment periods. The corresponding date of incident self-harm was identified as the event date.

Statistical analysis

The association between gabapentinoid treatment and self-harm was calculated by comparing the incidence of self-harm during different risk periods with that during reference periods. Adjusted incidence rate ratio and the corresponding 95% confidence intervals (CIs) were estimated using conditional Poisson regression, adjusted for age, season, and concomitant opioids and psychotropic medications (supplementary table

3-6). Results were stratified by age groups, sex, ethnic groups, types of gabapentinoid, and status of different comorbidities, Including bipolar and mania, depression, anxiety disorder, schizophrenia, other psychosis, and insomnia (appendix 2).

We conducted a comparison analysis between pregabalin-only and gabapentin-only treatment periods in patients who took both medications during the observation period (appendix 2). Sixteen levels of risk windows were created to account for all possible combinations of gabapentin and pregabalin usage because each drug has four risk windows (before, during, after treatment, and reference periods). The incident rate of self-harm during the pregabalin only treatment period was compared with the gabapentin only treatment period. We also did an interaction study between gabapentinoid and opioid (appendix 2). The incident rate of self-harm during different risk windows was compared with the one at reference period (supplementary figure 2). A secondary analysis was also performed by redefining the start of observation period to 90 days after the first self-harm event and evaluating the recurrent rate of self-harm (figure 1).

Ethnic groups were categorised into six groups: black, East Asian, South Asian, white, other, and missing. Around 90% of the included patients had recorded ethnic group from Hospital Episode Statistics. For the remaining patients, ethnic group was classified, based on the SNOMED-CT code from Clinical Practice Research Datalink Aurum (supplementary table 7). Patients recorded as black African, black Caribbean, or black other were classified as "black"; patients recorded as Chinese or other Asian were classified as "East Asian"; patients recorded as Bangladeshi, Indian, or Pakistani were classified as "South Asian"; patients recorded as white were classified as "white"; and patients recorded as other or mixed were classified as "other." Patients who did not have their ethnic group recorded from both Hospital Episode Statistics and Clinical Practice Research Datalink Aurum were classified as "missing."

A two sided significance level of 5% was used in all statistical analyses. SAS (version 9.4) and R Foundation for Statistical Computing (version 4.2.0) were used for data manipulation and analysis.

Sensitivity and negative control analyses

Spline based self-controlled case series analysis[57] and more than 20 sensitivity analyses were prespecified to test the validity and robustness of the initial study results. The included sensitivity analyses accounted for potential exposure misclassification, outcome misclassification, confounding by indication, and the key assumptions of self-controlled case series model, specifically: the occurrence of the event does not influence subsequent exposures, and the event should not influence the length observation periods.[42 58] To ensure the robustness of our median imputation approach for gabapentinoid prescription duration, we conducted a sensitivity analysis using multiple imputation with chained equations, generating 10 datasets and pooling the estimates according to Rubin's rule.[59 60] Additionally, our sensitivity analyses examined synergistic effects of opioids and potential effects from the covid-19 pandemic. Subgroups were compared to examine the differences among them (supplementary table 16 to 20).[61] Detailed information about subgroups and sensitivity analyses is provided in appendices 2 and 3. We used negative control analysis using otitis media as an outcome to identify any residual confounders that may affect the results (appendix 3).

This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.[62]

Patient and public involvement

Patient and public involvement activities were funded by the patient and public involvement starter bursary from the University College London Hospitals and National Institute for Health and Care Research's Biomedical Research Centre. Meetings were held with patients who were prescribed gabapentinoids to refine the research question and select outcome measures. At the end of the study, the patients commented on the findings and contributed to the dissemination plan.

Table 1 | Patient characteristics

				Treatment periods		Non-treatment periods	
Characteristics	No. of Individuals (%)	Mean age at observation start, years (SD)	Median length of prescriptions (IQR) (days)	No. of events	Total follow-up time (patient years)	No. of events	Total follow-up time (patient years)
All	10 002 (100)	39.01 (14.92)	28 (7 to 28)	1878	19 442.09	8124	113 347.51
Female	6655 (66.54)	38.52 (14.90)	28 (7 to 28)	1183	12 928.63	5472	77 121.95
Male	3347 (33.46)	39.98 (14.92)	28 (7 to 28)	695	6513.46	2652	36 225.56
Gabapentin only	4767 (47.66)	39.40 (14.93)	28 (7 to 28)	739	7062.94	4028	56 033.62
Pregabalin only	3164 (31.63)	37.91 (15.31)	28 (7 to 28)	638	6034.01	2526	33 354.65
Used both gabapentin and pregabalin	2071 (20.71)	39.79 (14.20)	28 (14 to 28)	491	6294.26	1580	24 010.13
Black	143 (1.43)	35.83 (13.88)	28 (7 to 28)	25	233.26	118	1390.60
East Asian	85 (0.85)	35.45 (14.06)	28 (7 to 28)	17	130.70	68	749.56
South Asian	281 (2.81)	35.68 (12.22)	28 (7 to 28)	39	483.32	242	3452.22
White	9257 (92.55)	39.26 (15.03)	28 (7 to 28)	1751	18 210.23	7506	105 466.80
Mixed or others	188 (1.88)	35.64 (11.96)	28 (14 to 28)	30	322.00	158	1872.50
Missing ethnic group	48 (0.48)	38.15 (16.88)	28 (7 to 28)	16	62.59	32	415.84

IQR=interquartile range; SD=standard deviation.

Table 2 | Patient characteristics in relation to events. Values are numbers (percentages) unless stated otherwise

Variables	Study population (%) (n=10 002)
Mean (SD) age on event date (years)	45.63 (16.09)
Mean follow-up time (SD)	13.28 (6.12)
Use of gabapentinoids during observation period:	
Prescribed with gabapentin only	4767 (47.66)
Prescribed with pregabalin only	3164 (31.63)
Prescribed with both gabapentin and pregabalin	2071 (20.71)
Comorbidities throughout observation period:	
Neuropathic pain or chronic pain	6227 (62.26)
Bipolar and mania	617 (6.17)
Depression	8009 (80.07)
Anxiety disorders	5546 (55.45)
Schizophrenia	241 (2.41)
Other psychosis	443 (4.43)
Insomnia	2367 (23.67)
Any of the above mental health conditions	8819 (88.17)
Patients died within six months of event	149 (1.49)
Use of gabapentinoids six months before event:	
Gabapentinoids	2559 (25.58)
Gabapentin	1378 (13.78)
Pregabalin	1271 (12.71)
Use of other medications six months before event:	
Antiseizure medications	627 (6.27)
Opioids	4621 (46.20)
Hypnotics and anxiolytics	3790 (37.89)
Antidepressants	7105 (71.04)
Antipsychotics	1658 (16.58)
Any of the above medications	8448 (84.46)
Use of other medications prescriptions during observation period:	
Antiseizure medications	2117 (21.17)
Opioids	8971 (89.69)
Hypnotics and anxiolytics	7880 (78.78)
Antidepressants	9657 (96.55)
Antipsychotics	5433 (54.32)
Any of the above medications	9961 (99.59)

SD=standard deviation.

Results

Summary of characteristics

Between 1 January 2000 and 31 December 2020, 1 503 597 individuals received at least one prescription of gabapentinoids. Among them, 203 871 were younger than 18 years and were excluded. Of the remaining individuals, 425 448 had not received gabapentinoids within the observation periods, 864 273 did not have an incident self-harm event within the observation periods, and three had a first self-harm event on the first day of any exposed periods. Overall, 10 002 individuals were included in the analysis. Of these individuals, 6655 (66.54%) were female, the mean age at the start of observation was 39.01 years (standard deviation (SD) 14.92), and the mean duration of the follow-up per individual was 13.28 years (SD 6.12) (table 1 and table 2). The median length of each gabapentinoid prescription was 28 days (interquartile range 7-28 days) with an average gabapentinoid treatment person-time of 1.94 years in total per individual. Of the 10 002 individuals, 4767 (47.66%) took gabapentin only, 3164 (31.63%) took pregabalin only, and 2071 (20.71%) took both drugs during the observation period (table 2). Within the study period, 6227 (62.26%) individuals were diagnosed with neuropathic or chronic pain, and 8819 (88.17%) were diagnosed with bipolar disorder and mania, depression, anxiety disorders, schizophrenia, other psychosis, or insomnia. 8448 (84.46%) individuals were on neuropsychiatric medications six months before the event. Antidepressants (n=7105, 71.04%) were the most prescribed medication, followed by opioids (n=4621, 46.20%), and hypnotics and anxiolytics (n=3790, 37.89%). These were also the most prescribed medications throughout the observation period.

Main analysis results

The overall incidence of self-harm in the 1 503 597 individuals was 2.86 per 1000 patient years during gabapentinoid treatment periods. Of the 10 002 individuals included in the analysis, 615 incidents of self-harm occurred in the 90 days before treatment period, 1878 occurred during the treatment period, 130 occurred in the 14 days after treatment period, and 7379 took place in the reference period. The incidence rate of self-harm per 100 person years was 16.79 (95% CI 16.65 to 16.92) in the 90 days before treatment period, 9.66 (9.62 to 9.70) in the treatment period, 29.60 (29.09 to 30.11) in the 14 days after treatment period, and 6.75 (6.74 to 6.77) in the reference period (table 3). Risk of incidents of self-harm was increased during the 90 days before treatment (adjusted incidence rate ratio 1.69 (95% CI 1.55 to 1.85)) when compared with reference period (table 3, figure 2). The adjusted incidence rate ratio then decreased to 1.06 (95% CI 0.98 to 1.13) during the treatment period and increased again 14 days after treatment period (3.02 (2.53 to 3.60)). Further analysis using a non-parametric, spline-based method showed that the risk of self-harm reached its peak approximately 40 days before initiation of gabapentinoid treatment and decreased gradually afterwards (supplementary figure 3).

Subgroup analyses results

In the subgroup analyses, adjusted incidence rate ratios showed similar patterns to the main analysis (table 3, supplementary tables 8, 9, and 10 and supplementary figure 5) with the risk of self-harm during the treatment period lower or not higher than the 90 days before treatment period. Among individuals who were prescribed both gabapentin and pregabalin in the observation period, the incidence rate ratio of self-harm was higher but not statistically significant during pregabalin-only treatment periods when compared with gabapentin-only treatment periods (1.24 (95% CI 0.99 to 1.55)) (table 3). In the interaction studies, the adjusted incidence rate ratio of self-harm during concomitant use of gabapentinoids and opioids (0.98 (95% CI 0.88 to 1.10)) did not differ from the opioid-only treatment periods (0.94 (0.87 to 1.03)) (supplementary table 11).

Forest plot summarising the adjusted IRRs for self-harm associated with gabapentinoid use

Results are stratified by sex, types of gabapentinoids, and patients who took both gabapentin and pregabalin within observation period

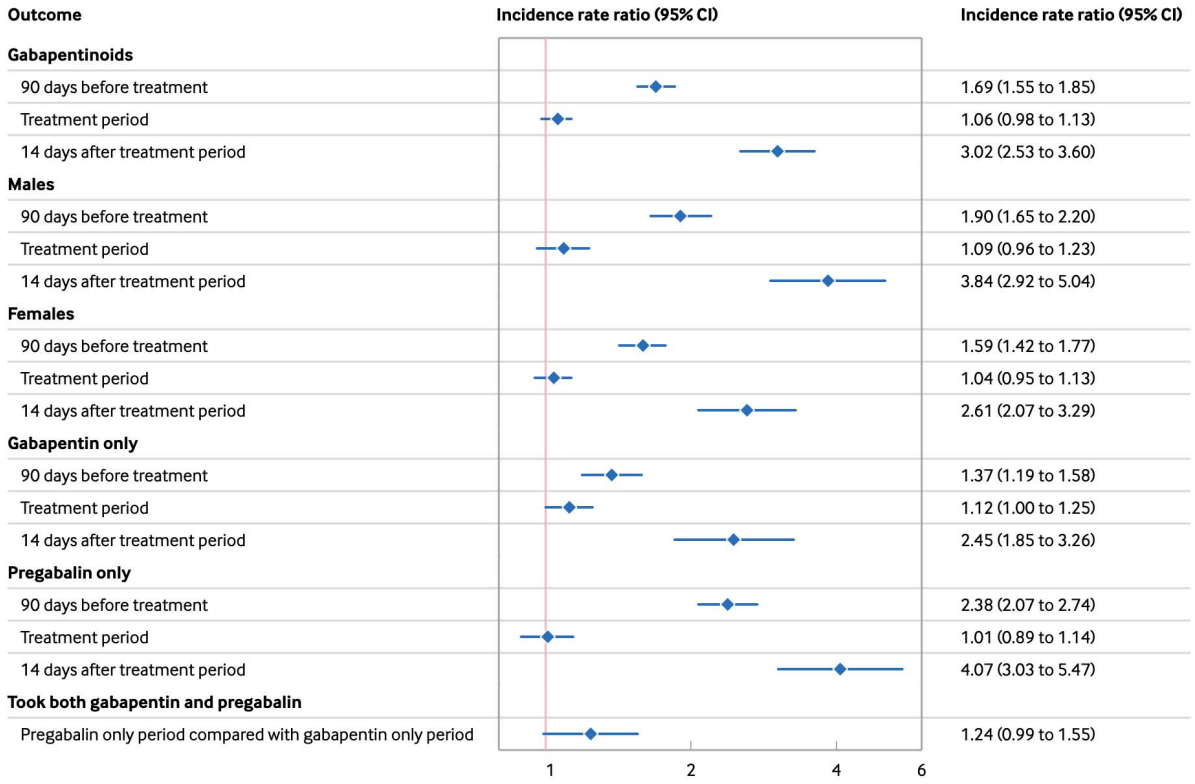

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Fig 2 | Forest plot summarising the adjusted IRRs for self-harm associated with gabapentinoid use, stratified by sex, types of gabapentinoids, and patients who took both gabapentin and pregabalin within the observation period. IRR=incidence rate ratio; CI=confidence interval. An interactive version of this graphic is available at https://public.flourish.studio/visualisation/22458780/

Secondary and sensitivity analyses

Secondary analysis, which looked into the risk of recurrent self-harm, showed a similar trend to the main analysis, with risks in the 90 days before and treatment periods attenuated towards null (supplementary table 12).

The majority of sensitivity analyses showed patterns consistent with the main analysis, with an increased risk of self-harm during the 90 days before treatment and no or a slight increase in the risk of self-harm during the treatment periods (supplementary table 13). When the first 28 days of treatment periods were defined as an additional risk window, an increased risk was observed (1.48 (1.28 to 1.71)) but the risk was not higher than the that in the 90 days before treatment period. A similar result was observed when the length of this period was extended to 120 days (1.33 (1.21 to 1.47)). Patients who did not receive opioids during the observation period showed a similar trend but with an increased risk in all risk windows (supplementary table 13). When using otitis media as a negative control outcome, no association was found during all risk periods when compared to reference period (supplementary table 13).

Discussion

Principal findings

In our study, compared with the reference period, the risk of incident self-harm increased during the 90 days preceding gabapentinoid treatment but began diminishing around the time of treatment initiation. After the gabapentinoid treatment period ended, the risk of self-harm markedly increased for approximately two weeks before returning to reference levels. Our results cannot rule out a potential risk of self-harm associated with gabapentinoid prescriptions, but the association does not seem to support a direct effect of

Table 3 | Results from the main study analyses, summarising the adjusted incidence rate ratios for self-harm associated with gabapentinoid use, stratified by sex, types of gabapentinoids (mutually exclusive)

Results	No. of events	Patient years	Crude incidence per 100 person years (95% CI)	Adjusted IRR (95% CI)	P value
Main analysis (n=10 002)					
90 days before treatment	615	3663.56	16.79 (16.65 to 16.92)	1.69 (1.55 to 1.85)	<0.001
Treatment period	1878	19442.09	9.66 (9.62 to 9.70)	1.06 (0.98 to 1.13)	0.14
14 days after treatment period	130	439.22	29.60 (29.09 to 30.11)	3.02 (2.53 to 3.60)	<0.001
Reference period	7379	109244.73	6.75 (6.74 to 6.77)	1.00 (1.00 to 1.00)	NA
Stratified by sex					
Female (n=6655):					
90 days before treatment	381	2503.01	15.22 (15.07 to 15.37)	1.59 (1.42 to 1.77)	<0.001
Treatment period	1183	12928.63	9.15 (9.10 to 9.20)	1.04 (0.95 to 1.13)	0.42
14 days after treatment period	74	301.28	24.56 (24.00 to 25.12)	2.61 (2.07 to 3.29)	<0.001
Reference period	5017	74317.66	6.75 (6.73 to 6.77)	1.00 (1.00 to 1.00)	NA
Male (n=3347)					
90 days before treatment	234	1160.56	20.16 (19.90 to 20.42)	1.90 (1.65 to 2.20)	<0.001
Treatment period	695	6513	10.67 (10.59 to 10.75)	1.09 (0.96 to 1.23)	0.16
14 days after treatment period	56	137.94	40.60 (39.54 to 41.66)	3.84 (2.92 to 5.04)	<0.001
Reference period	2362	34927.07	6.76 (6.74 to 6.79)	1.00 (1.00 to 1.00)	NA
Stratified by types of gabapentinoids (mutually exclusive)					
Gabapentin only (n=4767):					
90 days before treatment	225	1589.68	14.15 (13.97 to 14.34)	1.37 (1.19 to 1.58)	<0.001
Treatment period	739	7062.94	10.46 (10.39 to 10.54)	1.12 (1.00 to 1.25)	0.04
14 days after treatment period	50	196.69	25.42 (24.72 to 26.13)	2.45 (1.85 to 3.26)	<0.001
Reference period	3753	54247.25	6.92 (6.90 to 6.94)	1.00 (1.00 to 1.00)	NA
Pregabalin only (n=3164)					
90 days before treatment	261	937.17	27.85 (27.51 to 28.19)	2.38 (2.07 to 2.74)	<0.001
Treatment period	638	6034.01	10.57 (10.49 to 10.66)	1.01 (0.89 to 1.14)	0.90
14 days after treatment period	48	100.51	47.76 (46.41 to 49.11)	4.07 (3.03 to 5.47)	<0.001
Reference period	2217	32316.97	6.86 (6.83 to 6.89)	1.00 (1.00 to 1.00)	NA
Used both gabapentin and pregabalin within observation period (n=2071)					
Time under treatment of pregabalin only and gabapentin at reference period	274	3398.31	8.06 (7.97 to 8.16)	1.24 (0.99 to 1.55)	0.06
Time under treatment of gabapentin only and pregabalin at reference period (reference)	175	2536.73	6.90 (6.80 to 7.00)	1.00 (1.00 to 1.00)	NA

IRR=incidence rate ratio; CI=confidence interval; NA=not applicable. *All estimates are adjusted for age in one year age band, seasonal effect, opioids and psychotropic medications.

gabapentinoid treatment on self-harm because of the elevated risks observed before treatment initiation. This finding was further supported by the spline-based self-controlled case series analysis, which showed a rise in self-harm risk shortly before treatment, followed by a gradual decrease around the time of treatment initiation. Inclusion of an additional risk window of the first 28 or 120 days of treatment periods also showed a similar trend. The results are generalisable across sex, age, types of gabapentinoids, and different underlying psychiatric comorbidities.

In individuals who had received both gabapentin and pregabalin, the incidence rate of self-harm during pregabalin-only periods, while not statistically significant, was slightly higher than that during gabapentin-only periods, suggesting that the risk of self-harm may be higher with pregabalin treatment. In the interaction study, the addition of gabapentinoid to opioid treatment may not further increase the risk of self-harm. However, use of gabapentinoid in combination with opioids still cannot be confirmed as safe because our study focused solely on self-harm and previous studies have shown that concurrent use of gabapentinoids and opioids can lead to other adverse outcomes.[63-65]

To address the primary conditions that gabapentinoids are indicated for, we changed the start date of the observation period to the date of neuropathic pain or chronic pain diagnosis. The results in all risk periods were similar to the main analysis. Additionally, the results from the secondary analysis of recurrent self-harm showed a similar pattern to the main analysis. The results from other sensitivity analyses were also consistent with the main analysis. The negative control analysis using otitis media, which should not be associated with gabapentinoid treatment or underlying conditions, did not show the same risk patterns as in the primary or subgroup analyses. This suggests that the use of a self-controlled case series effectively addressed underlying risk and thus we can show the effect of the medication with minimal impact from different confounders.

Implications of the study

The increased risk of self-harm observed in the 90 days before treatment suggests that medical conditions related to the initiation of gabapentinoid may contribute to the increased risk of self-harm. The decision to start gabapentinoid treatment may be a response to changes in psychiatric problems

or worsening of underlying conditions. In addition, over 88% of the individuals included in the analyses were diagnosed with some forms of mental health condition, and more than 84% of them had at least one prescription six months before the outcome of antiseizure medications, opioids, hypnotics or anxiolytics or both, antidepressants, or antipsychotics. This indicates that many patients were already using pharmacological treatments for neuropsychiatric conditions, which may have precipitated the initiation of gabapentinoids and coincided with the elevation of self-harm risk. Clinical conditions, such as generalised anxiety disorder, bipolar disorder, or neuropathic pain, have been linked to an increased risk of self-harm in prior research.[66-68] The underlying conditions that gabapentinoids are used to treat may explain the higher risk of self-harm preceding gabapentinoid treatment.

However, we cannot attribute the eventual reduction in the risk of self-harm to the use of gabapentinoids because this decrease had already begun before gabapentinoid initiation. This reduction in risk can be attributed to reinforced care and the treatment of underlying diseases that can increase the risk of self-harm. Although we observed a reduction in self-harm around the time of gabapentinoid initiation, eventually returning to reference levels, the risk remains higher than reference period at the start of the treatment period. Therefore, extra attention to patients being treated is warranted.

The finding of increased risk of self-harm following gabapentinoid discontinuation also requires consideration. Previous reports and gabapentinoid labelling highlight that patients may exhibit agitation or suicidal behaviours as soon as a few days after discontinuation of treatment.[23 69-72] However, we cannot draw a causal link from our results to suggest that the spike in self-harm risk shortly after the treatment period is attributable to treatment cessation. Further research into this effect is warranted. The results show the necessity of close monitoring of patients during and after treatment use of gabapentinoid.

Strengths and weaknesses of this study

The increased risk of self-harm before and after treatment has not been previously observed and may have been missed in a classic cohort study in which patients with either events or exposures before the commencement of the study are usually excluded. The use of a large population based database provided sufficient statistical power to evaluate the association between gabapentinoid use and self-harm. The nature of the self-controlled case series design allowed for controlling for time invariant confounders by comparisons within individuals.[43] Time varying confounders, such as age, season, and concomitant medications were also adjusted in the conditional Poisson regression models.

Several limitations apply to our study. Firstly, Clinical Practice Research Datalink data include prescription but not dispensing or adherence information, which could lead to misclassification of exposure periods. However, the sensitivity analyses extending exposure by 1-10 weeks or analysing individuals with two or more prescriptions yielded results consistent with the main and spline-based analysis. Secondly, the database can only capture prescriptions that were issued by the general practitioner. Gabapentinoids prescribed in secondary or tertiary care, or obtained through illegal means are not recorded in the database. Thirdly, identifying self-harm cases using hospital records may result in an underestimate of numbers because only people with severe presentation would be admitted to hospital. One of the sensitivity analyses that also included self-harm diagnoses from primary care has shown a similar trend to our main analysis. We applied a within-individual design, the individual baseline risk should not affect our results and conclusion, and this would only affect statistical power rather than the interpretation of the result. Fourthly, patients were censored with epilepsy, cancer, or substance misuse diagnoses in our analyses. Interpretation of the results should not apply to patients with these conditions due to differences in drug usage patterns. Finally, similar to other observational studies, we cannot rule out the effect of other unmeasured time varying confounders such as transient socioeconomic status and use of illicit drugs. Nonetheless, results from the negative control analysis showed that our results are unlikely to be biased by residual confounders.

Comparison with other studies

Previous studies have reported conflicting results related to the association between gabapentinoids and the risk of self-harm attempts or behaviours.[25-31] Different study methods were adopted in these studies but they either compared gabapentinoids with other antiseizure drugs, grouped gabapentinoid with other antiseizure medications, were limited to a specific group of patients, or did not adjust important time varying covariates. By adopting the self-controlled case series design in this study, we have controlled all time constant covariates varying between individuals. Important time varying covariates such as age, season, and concomitant use of opioids and psychotropic medications were also adjusted in the analysis. Before treatment and after treatment cessation periods were included in our study design to address the potential effect of confounding by indication, which were unaccounted for in the previous studies. Multiple subgroups and sensitivity analyses have also further validated our main analysis.

One of the major advantages of the self-controlled case series design is that we were able to investigate the timing of the occurrence of an event of interest. By adopting a spline-based analysis, we identified that the highest risk of self-harm occurs around the time of gabapentinoid initiation and after treatment cessation, which highlights the importance of reinforced care and attention to patients from the start of the gabapentinoid treatment period and including after discontinuation.

Unanswered questions and future research

While our study provides valuable insights into the association between gabapentinoid treatment and self-harm risks, important questions that necessitate further exploration have arisen. Future studies may delve into the neurochemical pathways influenced by gabapentinoids, particularly their impact on mood and behaviour during and after treatment. Additionally, the elevated risk of self-harm shortly after treatment cessation warrants further investigation. Understanding the predictors of the risks in specific demographic groups could lead to more personalised treatment approaches. Although our study included stratified analyses for different subgroups, the interpretability of these results may be limited by the small sample sizes within some groups. Further validation using other healthcare databases could provide a more comprehensive understanding of how gabapentinoids affect diverse populations. Research into these areas could be of value for enhancing the safety of gabapentinoids, ensuring that they are prescribed optimally to maximise patient health benefits while minimising risks.

Conclusion

In this self-controlled case series study, we observed that the association of gabapentinoids and risk of self-harm is multifaceted, and the association does not support a direct effect of gabapentinoid treatment on self-harm. The risk of self-harm was increased shortly preceding gabapentinoid initiation. While the risk began to diminish around the time of gabapentinoid initiation, risk remained higher than reference levels, emphasising the need for reinforced care and attention to patients during this period. The marked increase in self-harm risk shortly after treatment cessation also highlights the importance of monitoring patients even after discontinuation. Our findings underscore the necessity for close patient monitoring of self-harm throughout the gabapentinoid treatment journey.

AUTHOR AFFILIATIONS

[1]Research Department of Practice and Policy, School of Pharmacy, University College London, London, UK

[2]Centre for Medicines Optimisation Research and Education, University College London Hospitals NHS Foundation Trust, London, UK

[3]School of Pharmacy, Aston University, Birmingham, UK

[4]Centre for Safe Medication Practice and Research, Department of Pharmacology and Pharmacy, Li Ka Shing Faculty of Medicine, University of Hong Kong, Hong Kong, Hong Kong

[5]Division of Psychiatry, University College London, London, UK

[6]Camden and Islington NHS Foundation Trust, London, UK

[7]East London Foundation NHS Trust, Bedfordshire, UK

[8]Institute of Psychiatry, Psychology and Neuroscience, King's College London, UK

[9]Laboratory of Data Discovery for Health (D24H), Hong Kong Science Park, Pak Shek Kok, Hong Kong

[10]School of Pharmacy, Medical Sciences Division, Macau University of Science and Technology, Taipa, Macau

[11]Advance Data Analytics for Medical Science Limited, Hong Kong, Hong Kong

Contributors: ASCY, BC, and KKCM had full access to the aggregate analysis data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. KKCM was responsible for the study concept, and KKCM and ASCY were responsible for the study design. ASCY and BC did the statistical analysis. ASCY and KKCM drafted the manuscript. ASCY, BC, AYLC, JFH, DPJO, FMCB, ICKW, WCYL, LW, and KKCM critically revised the manuscript for important intellectual content. ASCY and KKCM are the guarantors of this study. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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Ethical approval: The study protocol was approved via the Clinical Practice Research Datalink Research Data Governance Process (protocol number: 23_002896).

Data sharing: Application of further access to the study data are required from the UK Clinical Practice Research Datalink Research Data. Statistical code has been made publicly available at: https://github.com/andrewyuen97/GABA_self-harm_SCCS. No additional data available.

Patient consent: Detail has been removed from these case descriptions to ensure anonymity. The editors and reviewers have seen the detailed information available and are satisfied that the information backs up the case the authors are making. Participant consent is not required for Clinical Practice Research Datalink studies using purely observational and anonymised data.

Transparency: The lead authors (ASCY and KKCM) affirm that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Dissemination to participants and related patient and public communities: The results of the study will be disseminated to the patients who participated in the Patient and public involvement

activities and to the funder that supported these initiatives. A lay summary intended for dissemination is included in appendix 4.

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Web appendix: Extra material supplied by authors