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Trends in gabapentinoid prescribing in patients with osteoarthritis: a United Kingdom national cohort study in primary care

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SUMMARY

Objective: To investigate trends in gabapentinoid prescribing in patients with osteoarthritis (OA).
Methods: Patients aged 40 years and over with a new OA diagnosis recorded between 1995 and 2015 were identified in the Clinical Practice Research Datalink (CPRD) and followed to first prescription of gabapentin or pregabalin, or other censoring event. We estimated the crude and age-standardised annual incidence rates of gabapentinoid prescribing, stratified by patient age, sex, geographical region, and time since OA diagnosis, and the proportion of prescriptions attributable to OA, or to other conditions representing licensed and unlicensed indications for a gabapentinoid prescription.
Results: Of 383,680 newly diagnosed OA cases, 35,031 were prescribed at least one gabapentinoid. Irrespective of indication, the annual age-standardised incidence rate of first gabapentinoid prescriptions rose from 1.6 [95% confidence interval (CI): 1.3, 2.0] per 1000 person-years in 2000, to 27.6 (26.7, 28.4) in 2015, a trend seen across all ages and not explained by length of follow-up. Rates were higher among women, younger patients, and in Northern Ireland, Scotland and the North of England. Approximately 9% of first prescriptions could be attributed to OA, a further 13% to comorbid licensed or unlicensed indications.
Conclusion: Gabapentinoid prescribing in patients with OA increased dramatically between 1995 and 2015. In most cases, diagnostic codes for licensed or unlicensed indications were absent. Gabapentinoid prescribing may be attributable to OA in a significant proportion but evidence for their effectiveness in OA is lacking. Further research to investigate clinical decision making around prescribing these expensive and potentially harmful medicines is recommended.

Introduction

Over the last decade gabapentinoid (gabapentin and pregabalin) prescribing has increased substantially. In the United Kingdom (UK), prescriptions for gabapentin increased from fewer than 3 million to 7.8 million, and for pregabalin from 2.1 million to 6.7 million between 2010 and 2016[1–4], with similar patterns seen in other countries[5]. This increase in community prescribing within the UK may not only be accounted for by an increase in the number of gabapentinoids prescribed to existing users (likely due to a longer duration of therapy), but also by an increase in the number of patients prescribed them, with a recent study reporting that the rate of patients in the UK newly treated with either gabapentin or pregabalin has tripled between 2007 and 2017[6].

In the UK, gabapentin and pregabalin are licensed for epilepsy and neuropathic pain, and pregabalin also for generalised anxiety disorder[7]. They have been recommended as first-line treatments for neuropathic pain since 2013, although evidence of efficacy is based largely on trials in post-herpetic neuralgia and painful diabetic neuropathy[8,9]. Limited evidence exists for efficacy of pregabalin in fibromyalgia[10] but evidence in other painful conditions is lacking[11,12]. Nevertheless, 'off-label' gabapentinoid prescribing for painful conditions is common[5,6]. In 2017, more than 50% of UK gabapentinoid prescriptions were attributed to unlicensed indications[6]. Non-neuropathic, painful conditions may account for around 80% of unlicensed gabapentin and 50% of unlicensed pregabalin prescriptions[6]. This study explores the potential contribution of prescribing for osteoarthritis pain to the increase in gabapentinoid prescribing.

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Osteoarthritis (OA) is one of the most common painful musculoskeletal conditions worldwide[13]. OA guidelines internationally recommend a range of pharmacological treatments but not gabapentin or pregabalin[14–16]. Four small trials of pregabalin in OA have been published[17–20]. Whilst all identified a potential role for pregabalin in some patients with OA, there was no follow-up beyond 13 weeks. Despite this, anecdotal reports suggest that clinicians may prescribe gabapentinoids for "pain from osteoarthritis"[5]. Concerns about perceived lack of effectiveness, adverse events, and safety concerns with recommended pharmacological treatments, poor access to non-pharmacological therapies and literature suggesting a neuropathic component to some OA pain may all contribute[21–28].

To our knowledge, no studies to date have investigated gabapentinoid prescribing rates specifically in patients with osteoarthritis, or explored what proportion of gabapentinoid use may be for osteoarthritis pain. Our analysis of national UK primary care electronic health record data addresses these evidence gaps.

Methods

Data source

This was an observational epidemiological cohort study of data from the Clinical Practice Research Datalink (CPRD)'s GOLD dataset, a UK primary care database of routinely collected data from practices using the VISION software system. As of June 2017 the GOLD dataset collected data from 693 contributing practices, with information from 14.2 million patients available, of which 2.8 million were active[29]. Anonymised information available includes patient demographics, consultations, diagnoses and prescriptions. Diagnoses and changes in management made in secondary care will also be included in the CPRD providing letters are communicated to the general practice and recorded appropriately. Equally, if a medication started in secondary care was continued as a repeat prescription by the general practitioner (who is largely responsible for a patient's ongoing prescription), this would appear in the CPRD. Therefore, only one-off prescriptions issued in secondary care and not continued by the general practitioner may be missed by the CPRD. However, as OA is a chronic condition and predominantly managed in the community, this would be a rare occurrence.

Practices contributing data to the CPRD are representative of practices throughout the UK (approximately 7% of the UK population as of 2013)[30], and the diagnostic coding, upon which research is carried out, has been validated for a number of diagnoses, including musculoskeletal conditions (although not including OA[31]). Our study was approved by the Independent Scientific Advisory Committee (ISAC; protocol 18_007R). No further ethical permission was required, due to the nature of the analysis on anonymised data.

Study design

A cohort was assembled of patients with a new diagnosis of OA (first, index consultation) between 1st January 1995 and 31st December 2015. A patient's first diagnosis of OA was identified based upon the presence of an OA diagnostic Read code ('higher level' Read codes beginning N05, as used by prior studies[32,33] and which have high positive predictive value). This code list includes both joint specific codes, and more generalised OA codes where the site is not specified. Those with an OA-coded consultation or codes of hip or knee arthroplasty in the 3 years prior to the start of the study period were excluded; an efficient strategy for excluding prevalent cases of OA[34]. To reduce false positives during recruitment, and to ensure there was a temporal sequence between OA diagnosis and gabapentinoid prescription, we also excluded patients aged younger than 40 years at diagnosis as well as those patients who had received a gabapentinoid prescription in the 3 years prior to their index OA consultation, respectively. All OA codes used are available at www.keele.ac.uk/mrr/morbiditydefinitions/.

Patients were followed-up to the earliest of: gabapentinoid prescription, deregistering from their practice, death, practice no longer contributing data to the CPRD, or 31st December 2015. In the event that the gabapentinoid prescription occurred on the same date as another censoring event, the prescription was included in analyses.

Gabapentinoid prescriptions

Gabapentinoid prescriptions were identified by the presence of product codes in the cohort member's healthcare records. These product codes have been used previously in the CPRD[35], which were checked by an academic pain specialist and an academic general practitioner.

Indications for gabapentinoid prescribing

Within the UK general practitioners are encouraged to record a diagnostic code upon a new diagnosis or change in therapy[36]. However, unlike in some electronic health record systems in other countries, there is no direct link between each prescription and the indication for which it was issued. Therefore, in order to appreciate the proportion of first gabapentinoid prescriptions prescribed to patients with OA attributable to this condition, rather than to comorbidities, required identification of these comorbid conditions representing licensed and common unlicensed indications for gabapentinoid use. Possible indications for the gabapentinoids were identified using the British National Formulary (BNF), national guidelines issued by the National Institute for Health and Care Excellence (NICE), as well as by conducting scoping reviews of off-label gabapentinoid use[7,35,37–40]. Licensed indications are as mentioned above, and identified unlicensed indications included alcohol withdrawal, attention deficit disorder, bipolar disorder, complex regional pain syndrome, fibromyalgia, menopausal hot flushes, migraine, panic disorder and restless legs syndrome. Code lists corresponding to these indications were sourced from a publically available clinical codes repository[41], as well as publications in the CPRD bibliography[42].

Statistical analyses

For the period between 1995 and 2015 we calculated crude annual incidence rates, expressed per 1000 person-years, of first gabapentinoid prescription (irrespective of indication) among OA cohort members. Lexis expansion, which allows the progression of cohort members through more than one time-dependent variable simultaneously, was used to produce crude incidence rates stratified by age group (40–49, 50–59, 60–69, 70–79, 80+ years), gender, and geographical region of the general practice. Rates were also stratified by time since index OA consultation (<5, 5–9, 10–14, >15 years), and incidence rates were age-standardised using the cohort of patients present at mid-2015 as the reference population. 95% confidence intervals (CIs) were calculated using Poisson regression. All analyses were conducted using SPSS version 24.

Assuming an annual incidence of 1 per 1000, we would require at least 47,023 person-years of observation within each calendar year to detect a difference of 0.5 per 1000 person-years, at the 95% confidence level with 80% power. Annual incidence rates after 2000 were based on person-time at risk greater than this although

estimates prior to 2000 and from stratified analyses (e.g., by geographical region) would have lower precision.

As per previous studies[6,43], the indication for each gabapentinoid prescription was identified using the Read codes recorded at or around the time of prescription. In the primary analysis, prescriptions were attributed to a condition providing the code was entered within the period from 14 days before to 90 days (−14 to +90) after the prescription date. Sensitivity analyses explored the effect of expanding this window to 6 months either side of prescription (−180 to +180) and then from 1 year before to 6 months after the gabapentinoid prescription date (−365 to +180). Six months following a patient's first prescription was chosen as this has been used in a prior study of pregabalin use within UK primary care[43]. If patients had more than one consultation date for the same indication, the consultation closest to their first prescription date was chosen. As a result, whilst patients could have Read codes of numerous indications, they could only have one code for each condition. Consequently, attribution in the primary analysis would also occur in the following sensitivity analyses. We expressed the results of this analysis in mutually exclusive categories. Prescriptions were attributed to (in order of precedence): licensed indication, unlicensed indication (not including OA), OA, and finally the proportion of prescriptions that remained unattributable.

Results

Our cohort comprised 383,680 patients newly diagnosed with OA between 1st January 1995 and 31st December 2015 (baseline characteristics: Table I). Median follow-up was 5.1 years (interquartile range (IQR): 2.3, 8.7), resulting in more than 2 million person-years of follow-up. 35,031 (9.1%) cohort members received a gabapentinoid prescription. First prescriptions were issued to patients with OA in all years of the study period, increasing from 2 in 1995, to 1163 in 2005, and finally to 3954 in 2015 (available in supplementary table). Of the 35,031 prescriptions, 25,208 (72%) were gabapentin (most common dose: 300 mg), the remainder pregabalin (most commonly 75 mg capsules).

Incidence rates

The crude incidence rate of first gabapentinoid prescriptions in this cohort, irrespective of indication, increased throughout the course of the study period, rising from less than 1 per 1000 person-years before 2000, to 9.5 (95% CI: 9.0, 10.1) in 2005, and to 28.0 (27.2, 28.8) in 2014. The crude incidence rate remained fairly constant in 2015 (27.9 (27.1, 28.8) first prescriptions per 1000 person-years). Age-standardisation resulted in very similar rates and trend. Incidence rates were similar between age groups until 2005, but thereafter the incidence rate of first gabapentinoid prescription was consistently highest in those aged 40–49 years, and lowest in those aged ≥80 years (Table II). The incidence of gabapentinoid prescribing increased throughout all strata of time since diagnosis, but was most pronounced in those who received their prescription within 5 years of their index consultation (available in supplementary table).

From the mid-2000s the age-standardised incidence rate of first prescriptions was higher in females than in males. Rates increased in females and males from 10.2 (9.5, 10.9) and 8.4 (8.0, 8.8) in 2005, through 18.8 (18.0, 19.6) and 15.2 (14.6, 15.9) in 2010, to 30.6 (29.5, 31.8) and 23.0 (22.0, 24.0) in 2015, respectively. Throughout the study period, there was an increase in the age-sex standardised incidence rate of first gabapentinoid prescriptions in all 13 geographical regions of the CPRD. However, regions with a relatively high incidence compared to the remainder of the UK included Northern Ireland, Scotland and the North East and North West of England (Fig. 1).

Table I
Characteristics of patients newly diagnosed with osteoarthritis between 1995 and 2015

Characteristic	Total patients with OA (n = 383,680)
Female gender, *n* (%)	234,159 (61.0)
Age stratification, *n* (%)	
40–49 yr	33,778 (8.8)
50–59 yr	88,120 (23.0)
60–69 yr	111,053 (28.9)
70–79 yr	95,506 (24.9)
80+ yr	55,223 (14.4)
Geographical region, *n* (%)	
North East	8443 (2.2)
North West	50,390 (13.1)
Yorkshire & Humber	17,710 (4.6)
East Midlands	17,535 (4.6)
West Midlands	41,205 (10.7)
East of England	34,664 (9.0)
South West	33,674 (8.8)
South Central	36,843 (9.6)
London	28,124 (7.3)
South East Coast	32,998 (8.6)
Northern Ireland	10,817 (2.8)
Scotland	31,547 (8.2)
Wales	39,730 (10.4)
Ethnicity, *n* (%)	
Not recorded	262,820 (68.5)
White	115,872 (30.2)
Other ethnic group	4988 (1.3)
Charlson Index of Comorbidity, *n* (%)	
HIV/AIDS	1 (0.0)
Cancer	2292 (0.6)
Cerebrovascular diseases	1328 (0.3)
Chronic pulmonary diseases	3672 (1.0)
Coronary heart disease	1037 (0.3)
Dementia	590 (0.2)
Diabetes mellitus	2372 (0.6)
Diabetes with complications	655 (0.2)
Hemiplegia and paraplegia	54 (0.0)
Metastatic tumour	148 (0.0)
Mild liver disease	113 (0.0)
Moderate or severe liver disease	27 (0.0)
Myocardial infarction	1097 (0.3)
Peptic ulcer disease	743 (0.2)
Peripheral vascular disease	871 (0.2)
Renal disease	3020 (0.8)
Rheumatological disease	1102 (0.3)

Attribution

4163 (11.9%) of the 35,031 patients prescribed a gabapentinoid had a code for a licensed indication within −14 to +90 days of the date of their first gabapentinoid prescription (Fig. 2). This attribution was largely due to neuropathic pain (4058 (97%), of which 1291 were sciatica). As patients could have codes for more than one licensed indication, there were 4176 codes given to this group of patients during this time. A further 543 (1.6%) first gabapentinoid prescriptions could be attributed to an unlicensed indication, of which fibromyalgia and restless legs syndrome were the most common. The proportion of first prescriptions attributed to a licensed or unlicensed indication was similar by gender, but slightly higher in older patients (10.8% in those aged 40–49 years, compared to 14.8% in those aged over 80 years).

3303 (9.4%) of the 35,031 patients prescribed a gabapentinoid had a diagnostic code for OA entered within −14 to +90 days of the date of gabapentinoid prescription with no code for a licensed or unlicensed indication. Whilst the proportion

Table II
Crude incidence rate of first gabapentinoid prescriptions by patient age group, and age-standardised incidence rate

Year	Age group										Age standardised	
	40–49 years		50–59 years		60–69 years		70–79 years		80 years and over			
	IR	95% CI	IR	95% CI	IR	95% CI	IR	95% CI	IR	95% CI	IR	95% CI
1995	0.00	(0.00, 10.83)	2.61	(0.32, 9.42)	0.00	(0.00, 3.46)	0.00	(0.00, 3.37)	0.00	(0.00, 6.33)	0.36	(0.00, 0.85)
1996	1.03	(0.03, 5.75)	0.42	(0.01, 2.33)	0.30	(0.01, 1.65)	0.30	(0.01, 1.66)	0.00	(0.00, 1.84)	0.26	(0.01, 0.51)
1997	0.67	(0.02, 3.71)	0.24	(0.01, 1.33)	0.00	(0.00, 0.62)	0.00	(0.00, 0.61)	0.00	(0.00, 1.02)	0.05	(0.00, 0.12)
1998	0.52	(0.01, 2.89)	0.50	(0.10, 1.45)	0.23	(0.03, 0.83)	0.11	(0.00, 0.62)	0.19	(0.00, 1.05)	0.23	(0.07, 0.39)
1999	0.43	(0.01, 2.41)	0.51	(0.14, 1.30)	0.71	(0.31, 1.40)	0.50	(0.18, 1.09)	0.28	(0.03, 1.02)	0.50	(0.29, 0.72)
2000	4.62	(2.46, 7.90)	1.72	(1.00, 2.76)	1.21	(0.70, 1.93)	1.70	(1.10, 2.50)	1.59	(0.89, 2.62)	1.61	(1.27, 1.95)
2001	4.02	(2.14, 6.88)	2.70	(1.85, 3.82)	2.63	(1.91, 3.53)	2.35	(1.68, 3.18)	2.88	(1.99, 4.02)	2.66	(2.25, 3.06)
2002	4.55	(2.65, 7.28)	4.60	(3.54, 5.87)	4.66	(3.76, 5.72)	4.65	(3.77, 5.68)	3.62	(2.70, 4.75)	4.38	(3.90, 4.86)
2003	7.55	(5.17, 10.67)	6.20	(5.06, 7.51)	5.66	(4.74, 6.70)	6.39	(5.43, 7.48)	5.12	(4.11, 6.31)	5.86	(5.35, 6.37)
2004	6.72	(4.63, 9.44)	6.87	(5.77, 8.13)	7.19	(6.24, 8.24)	7.28	(6.33, 8.33)	6.23	(5.20, 7.40)	6.92	(6.41, 7.42)
2005	10.38	(7.90, 13.39)	9.23	(8.03, 10.55)	9.80	(8.78, 10.90)	9.40	(8.40, 10.49)	9.46	(8.28, 10.75)	9.53	(8.98, 10.08)
2006	13.57	(10.84, 16.78)	10.62	(9.39, 11.97)	9.57	(8.63, 10.59)	10.79	(9.78, 11.88)	9.43	(8.32, 10.64)	10.14	(9.61, 10.67)
2007	13.44	(10.81, 16.53)	11.79	(10.53, 13.17)	12.35	(11.34, 13.42)	12.67	(11.63, 13.78)	11.24	(10.09, 12.49)	12.11	(11.56, 12.66)
2008	18.01	(15.01, 21.43)	15.11	(13.71, 16.62)	13.34	(12.33, 14.40)	14.86	(13.78, 16.01)	11.99	(10.85, 13.21)	13.80	(13.24, 14.37)
2009	20.05	(16.92, 23.59)	16.56	(15.11, 18.10)	15.38	(14.34, 16.48)	16.03	(14.94, 17.18)	13.39	(12.22, 14.63)	15.34	(14.77, 15.92)
2010	28.95	(25.18, 33.12)	19.89	(18.31, 21.56)	17.50	(16.41, 18.64)	17.45	(16.32, 18.63)	14.73	(13.54, 16.01)	17.40	(16.80, 18.00)
2011	30.26	(26.36, 34.58)	23.98	(22.24, 25.81)	19.10	(17.97, 20.28)	20.70	(19.47, 21.98)	16.22	(14.98, 17.53)	19.79	(19.15, 20.43)
2012	36.53	(32.16, 41.32)	26.42	(24.59, 28.35)	19.32	(18.19, 20.50)	20.90	(19.68, 22.18)	16.86	(15.61, 18.17)	20.57	(19.93, 21.22)
2013	40.28	(35.51, 45.51)	29.04	(27.07, 31.11)	22.16	(20.93, 23.45)	24.53	(23.20, 25.93)	21.11	(19.69, 22.59)	24.00	(23.29, 24.71)
2014	48.49	(42.89, 54.63)	35.11	(32.84, 37.49)	24.50	(23.14, 25.93)	28.51	(27.02, 30.05)	23.78	(22.23, 25.41)	27.57	(26.78, 28.37)
2015	44.06	(38.20, 50.55)	34.89	(32.46, 37.46)	26.90	(25.36, 28.51)	26.61	(25.05, 28.23)	23.85	(22.18, 25.61)	27.57	(26.71, 28.43)

N.B. All incidence rates are displayed per 1000 person-years (IR: annual incidence rate, CI: confidence interval). Rates age-standardised against the cohort present in mid-2015.

of prescriptions attributed to OA was similar by patient gender and region, it was inversely proportional to age, with 17.1% of first prescriptions attributable to OA in those aged 40–49 years, compared to 7.9% in those aged 80 years or older. From 2001 onwards, when there were more than 100 first prescriptions annually, the proportion of prescriptions attributed to OA remained fairly constant (9–11%).

A large proportion (27,022; 77.1%) of first gabapentinoid prescriptions remained unattributed to OA or a licensed or unlicensed indication in our primary analysis. Expansion of the time window studied from −14 days to +90 days from first gabapentinoid prescription, to 6 months either side of prescription, and finally to 1 year prior to 6 months after first prescription did increase attribution to licensed and unlicensed indications (from 13.4%, to 22.3% and then to 26.1%, respectively). Attribution to OA also increased in the same time periods, from 9.4%, to 22.9% and finally to 28.2%. However, 45.8% of first prescriptions remained unattributed even when allowing for relevant codes from −365 days to +180 days from the date of gabapentinoid prescription. Throughout all time windows studied the relative proportion of first gabapentinoid prescriptions attributed to OA compared to both licensed and unlicensed indications remained fairly constant.

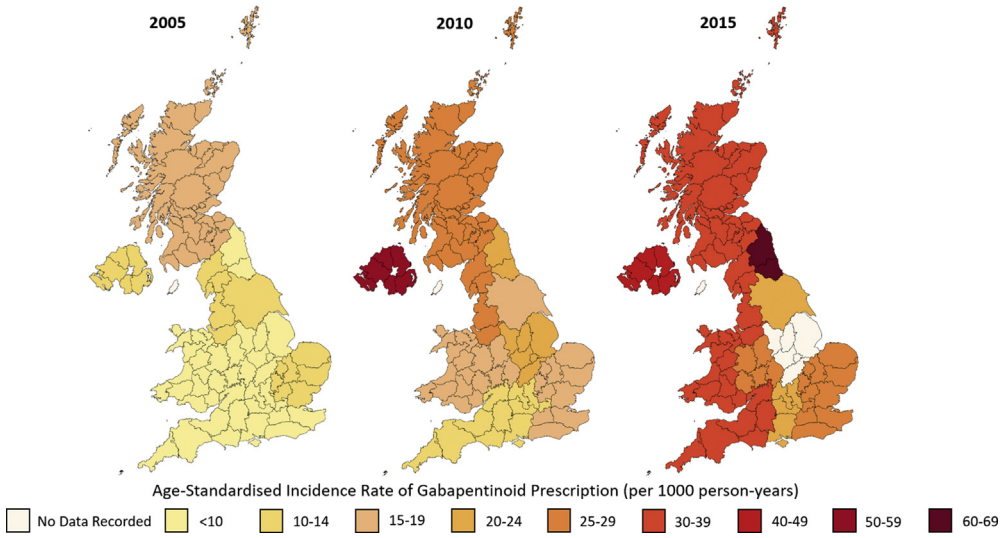

Fig. 1. Age-sex standardised incidence rate of gabapentinoid prescription, by geographical region.

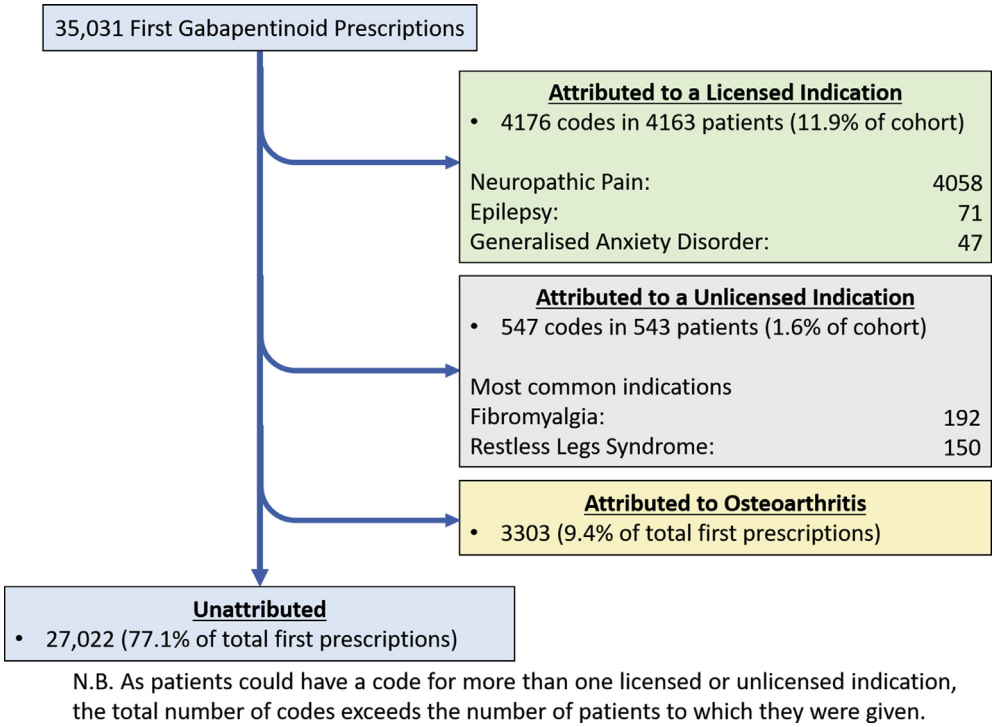

Fig. 2. Flow chart of attribution of first gabapentinoid prescriptions.

Discussion

Between 1995 and 2015 patients with OA have become increasingly likely to be prescribed a gabapentinoid. This increase in the incidence rate of gabapentinoid prescribing has been substantial and sustained. The age-standardised rate rose three-fold to 28 first gabapentinoid prescriptions per 1000 person-years between 2005 and 2015, and this is not explained by an increase in follow-up. Whilst this rising trend was evident for males and females of all ages and across all regions of the UK, those most likely to receive a gabapentinoid prescription were younger, female patients as well as those in Northern Ireland, Scotland and the North of England. 77% of first gabapentinoid prescriptions in this cohort of patients with OA did not have a relevant diagnostic code at or around the time of prescription. It is, therefore, difficult to establish precisely what proportion of gabapentinoid prescriptions are for OA related pain or for other comorbidities. However, our analysis found that the proportion of first gabapentinoid prescriptions attributable to OA (9%), was similar to the proportion attributable to licensed or other common unlicensed indications combined (13%).

Our study demonstrates a rising trend in gabapentinoid prescribing for patients with OA that mirrors the three-fold increase in prescribing across the general population[6]. Although a large proportion of gabapentinoid prescriptions could not be attributed to any indication in the primary analysis, our findings suggest that prescribing for pain associated with OA, a condition for which gabapentinoids are unlicensed and have limited evidence of efficacy, has contributed to the overall rise in gabapentinoid prescribing. Comparison to prior literature provides further context to this.

The attribution analysis in this study is similar to that of previous studies and therefore allows comparison. Like these prior studies, searching for codes within a narrow time window in relation to the gabapentinoid prescription date results in a large proportion of prescriptions unattributable to identified indications[43], with a larger, more sensitive window resulting in fewer unattributed prescriptions[6,43] (from 77.1% to 45.8% in our most sensitive analysis). However, this expansion requires the assumption that diagnostic codes entered weeks or months before or after prescription relate to its indication. Given this, the more conservative, narrow time window was used in our primary analysis. Furthermore, the use of mutually exclusive attribution categories, whereby patients with a prescription attributed to a licensed or unlicensed indication may also have had a code for OA in proximity to their prescription (but not attributed to OA) means that the presented contribution of OA is likely conservative.

Further comparison to prior literature demonstrates that the regional variation in prescribing rates is not exclusive to the gabapentinoids. For instance an English study of opioid consumption reported that nine out of the ten clinical commissioning groups with the highest opioid dose per head were in the North of England[44]. Another factor may be the influence of regional deprivation on prescribing rates. Whilst not specific to patients with OA, a UK based study of the prescribing of dependence forming medicines reported higher gabapentinoid prescribing across all conditions in areas with greater deprivation[35]. This report also found that the North East had low rates of long term gabapentinoid prescribing. This may not only reflect possible differences in prescribing in different conditions, but may demonstrate that this region has a high incidence of initiation of gabapentinoid prescribing, but short duration of use[35].

Our study has some limitations. First, although the CPRD is a nationwide dataset and representative of the UK as of the 2011 census[30], the GOLD dataset relies on software found in only 9% of practices, mainly focussed in Manchester, Birmingham, London and the South of England[45], which may affect generalisability. Second, our chosen definition of OA led to a smaller patient cohort and therefore the reported number of patients with OA prescribed a gabapentinoid is likely to be a conservative estimate. We included only incident OA, thus excluding a small number of patients who

consulted for OA in the 3 years prior to the study period beginning, to allow the calculation of person-time as well as a patient's time since diagnosis. We defined OA using diagnostic OA codes only, rather than including symptom codes such as 'joint pain', to minimise false positives. Using symptom codes may have given a cohort three times larger[34]. However, using diagnostic codes improved our ability to distinguish gabapentinoid prescriptions for OA from other indications, such as fibromyalgia and neuropathic pain, in the attribution analysis. Diagnostic codes are more likely to be used to record OA in older patients with more severe disease[46], approximately 10 years after their initial presentation for joint pain[47]. This may explain the apparently counterintuitive finding of a higher rate of prescribing in patients with a short time since diagnosis, given that, in clinical practice, one might expect clinicians to utilise recommended therapies first.

Third, we were unable to attribute a large proportion of gabapentinoid prescriptions to any indication, leaving considerable uncertainty over the amount of prescribing specifically for the control of OA pain. A large proportion of prescriptions remained unattributed even in our most sensitive analysis, which may reflect a lack of diagnostic coding by primary care practitioners, therefore suggesting that the guidance on entering diagnostic codes upon a change in management is often not followed in practice. Other contributing factors to low attribution could be the use of codes by practitioners not included in our code lists and other unlicensed conditions not identified by the scoping reviews. For instance we have documented a declining trend in the recording of OA using diagnostic codes[48], which may not only have reduced cohort recruitment in recent years, but also lead to an under-estimation of the proportion of gabapentinoid prescriptions attributable to OA during this time. A relatively stable proportion of first prescriptions were attributed to OA across the study period, a surprising finding, which is at odds with our hypotheses that rising gabapentinoid prescribing for patients with OA may be driven by growing concerns about currently recommended therapies, such as opioids, and by emerging evidence suggesting that OA pain may have a neuropathic component. A declining trend in the recording of OA in primary care could, in part, explain this. However, attribution of first prescriptions to licensed or unlicensed indications also remained fairly consistent throughout the study period, suggesting systematic under-recording of diagnoses by clinicians across all conditions. Another explanation may be that use of non-recommended therapies to treat pain associated with OA predates more recently emerging evidence and is driven primarily by a lack of effective treatment options. As the proportion of first gabapentinoid prescriptions attributed to OA relative to other indications, even in our sensitivity analyses, remained fairly constant, we believe this provides evidence that, despite evidence of under-recording, osteoarthritis is an important cause of gabapentinoid prescription.

OA is a common condition with a rising prevalence and therefore the potential impact of the observed rising trend in gabapentinoid prescribing for patients with OA is substantial both in terms of healthcare costs and potential harm to patients. In 2015, the UK National Health Service spent over £31 million on Gabapentin and £280 million on Pregabalin prescribing in England alone[2]. Given the lack of evidence to support the effectiveness of gabapentinoids for OA pain, more patients may be exposed to the potential harms of gabapentinoids without useful benefit. Side effects are commonly reported in patients using gabapentin or pregabalin. These include, among others, somnolence and dizziness[49], which may be particularly problematic in patients with OA, as they may reduce exercise and activity, and increase the risk of falls. Patients with OA may also be prescribed other analgesics, including opioids, which may interact with the gabapentinoids resulting in a greater sedative effect, and increase the risk of respiratory depression[50].

Further harm from gabapentinoid prescribing arises from their potential for misuse[49,51–53], with increasing reports in recent years of both gabapentin and pregabalin being associated with overdoses and deaths. This has culminated in both gabapentinoids becoming controlled medications in the UK from 1st April 2019[54]. Studies of gabapentinoid misuse have demonstrated that the risk of misuse in the general population appears low, with the highest risk being in populations with substance abuse disorders and prison inmates[49]. An association between overall gabapentinoid prescribing and gabapentinoid-related deaths has been reported[53] and the high prevalence of OA has the potential to substantially increase the supply of prescribing gabapentinoids available for diversion in the community. Given the potential for harms and the high proportion of prescriptions that cannot be attributed to a licensed indication, understanding the determinants of off-label gabapentinoid prescribing is important. We therefore encourage the replication of our analyses in other administrative and clinical patient electronic health record databases, particularly those with mandatory recording of indications for prescriptions, in conjunction with the investigation of the factors that may influence clinical decision making resulting in the prescription of a gabapentinoid.

In conclusion, in the UK, there has been an increase in the likelihood of patients with OA being prescribed a gabapentinoid. Our analysis suggests that a proportion of gabapentinoid prescribing may be for pain associated with OA and therefore that prescribing for OA may have contributed to the general rise in gabapentinoid prescribing in the UK. Given the potential for harm and limited evidence of efficacy for their use for OA pain, gabapentinoid prescribing for this common, painful condition requires careful justification by clinicians. Further research to investigate clinical decision making around prescribing these medicines is recommended.

Author contributions

GP, JA, and JB conceived the study; all authors contributed to the study design; TA and DY conducted the analysis of data; all authors contributed to the interpretation of results; all authors commented on manuscript drafts and approved it prior to submission.

Conflicts of interest

The authors have no conflicts of interest to declare.

Role of funding

N/A.

Disclaimer

This study is based in part on data from the CPRD GOLD database obtained under licence from the UK Medicines and Healthcare products Regulatory Agency. However, the interpretation and conclusions contained in this report are those of the author/s alone.

Sponsor

N/A.

Ethics

Due to the nature of the descriptive analysis of anonymised data, ethical approval was not required. Approval for use of the CPRD was obtained from the Independent Scientific Advisory Committee (ISAC), protocol number 18_007R.

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Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.joca.2019.06.008.

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