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Prevalence, healthcare resource utilization and mortality of Lennox-Gastaut syndrome: retrospective linkage cohort study

Richard F.M. Chin [a,*], W. Owen Pickrell [b,c], Florent Guelfucci [d], Monique Martin [e], Rowena Holland [f]

[a] Muir Maxwell Epilepsy Centre, Child Life and Health, University of Edinburgh, Royal Hospital for Children and Young People, 50 Little France Crescent, Edinburgh BioQuarter, Edinburgh, EH16 4TJ, UK
[b] Neurology and Molecular Neuroscience Group, Institute of Life Science, Swansea University Medical School, Swansea University, Swansea, SA2 8PP, UK
[c] Neurology Department, Morriston Hospital, Swansea Bay University Health Board, Swansea, SA6 6NL, UK
[d] Value, Access & HEOR, Commercial Advisory Group, Syneos Health, 41/45 Boulevard Romain Rolland, 92120 Montrouge, Paris, France
[e] Evidence Synthesis, Modeling, Communications, Evidera, The Ark, 201 Talgarth Road, London W6 8BJ, UK
[f] Market Access and Health Economics and Outcomes Research, GW Pharma Ltd, 1 Cavendish Pl, Marylebone, London W1G 0QF, UK

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ABSTRACT

Purpose: To retrospectively investigate the prevalence, demography, antiseizure medication (ASM) usage, healthcare resource utilization (HCRU), and mortality of patients with Lennox-Gastaut syndrome (LGS) in primary and secondary care in the UK.

Methods: Patients with confirmed LGS were anonymously identified from the UK Clinical Practice Research Datalink (CPRD) GOLD database (01/01/1987–31/1b0/2018) using the LGS Read Code (F250500). Probable LGS was identified using the International Classification of Diseases-10/Read Code for epilepsy (Hospital Episode Statistics [HES]/CPRD) plus rufinamide prescription. Period prevalence was calculated based on patients enrolled in CPRD GOLD and alive in 2017. CPRD data were linked to HES to calculate HCRU, and to the Office for National Statistics mortality registry.

Results: Period prevalence of LGS was 0.578/10,000 (n = 180), with 74 and 106 patients identified with confirmed (0.289/10,000) and probable LGS (0.420/10,000). Mean (max) ASM usage was ~1 (3) per year. In confirmed LGS, valproate (72%), lamotrigine (69%), and clobazam (66%) were the most commonly prescribed ASMs. HCRU (per patient-year) was similar in confirmed and probable LGS and mostly consisted of primary care general practitioner consultations (4–6), outpatient visits (5–10), inpatient admissions (1–4), and A&E visits (1). During the follow-up period, 18 patients died with crude mortality rates of 6.12 (confirmed LGS) and 4.17 (probable LGS) deaths per 1000 person-years.

Conclusion: Prevalence of LGS appears low in the UK. The similarly high HCRU and mortality rates in confirmed and probable LGS support the validity and specificity of the probable LGS algorithm and high burden of LGS.

Abbreviations: ASM, antiseizure medication; CPRD, Clinical Practice Research Datalink; EMRs, electronic medical records; GP, general practitioner; HCRU, healthcare resource utilization; HES, Hospital Episode Statistics; HRA, Health Research Authority; ICD-10, International Classification of Diseases, 10th Revision; ILAE, International League Against Epilepsy; LGS, Lennox-Gastaut syndrome; NA, not applicable; NHS, National Health Service; ONS, Office for National Statistics; PPY, per patient-year; STROBE, Strengthening the Reporting of Observational Studies in Epidemiology; THIN, The Health Improvement Network.

* Correspondence: Muir Maxwell Epilepsy Centre, Child Life and Health, University of Edinburgh, Royal Hospital for Children and Young People, 50 Little France Crescent, Edinburgh BioQuarter, Edinburgh, EH16 4TJ, UK.

E-mail addresses: rchin@exseed.ed.ac.uk (R.F.M. Chin), w.o.pickrell@swansea.ac.uk (W.O. Pickrell), florent.guelfucci@syneoshealth.com (F. Guelfucci), martinmoniq@googlemail.com (M. Martin), RHolland@gwpharm.com (R. Holland).

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Introduction

Lennox-Gastaut syndrome (LGS) is a rare childhood-onset epileptic encephalopathy (1–10% of childhood epilepsy cases depending on age),[1] typically diagnosed in children under 8 years of age.[2] It is one of the most severe and difficult epileptic disorders to identify and manage[2,3] because of its highly variable presentation[1–3] and evolving features over time.[2,3] In addition, a number of seizure types may present at the onset of LGS,[2] often resistant to treatment,[2] resulting in variable outcomes following treatment.[4] In general, there is a poor prognosis for patients with LGS. Most patients require polytherapy,[5] live with seizures into adulthood,[6] and are at a high risk of developing an intellectual disability.[1] LGS is also associated with risk factors for sudden unexplained death in epilepsy[7] that underlie the 15% rate of early mortality.[8]

While developments have been made in understanding the etiology of LGS, there is a scarcity of data on the prevalence[9,10] and healthcare resource utilization (HCRU) in patients with LGS.[11] As LGS is a severe form of epilepsy with frequent intractable seizures,[6] it is likely that HCRU (eg general practitioner [GP] visits, secondary care referrals and hospitalizations) is high considering the increased HCRU in patients with epilepsy and increased seizure frequency.[12]

One of the reasons there are few studies reporting on the prevalence and HCRU in patients with LGS is the difficulty in identifying patients for population studies, partly because of the rarity of the syndrome,[13] difficulties in defining the syndrome,[14,15] and the historical absence of a method to record the diagnosis. While this is historically true, there are signs that more specific diagnoses are being made for patients previously diagnosed with epilepsy. For example, in the UK, the large decline in the cumulative and annual incidence of recorded epilepsy in primary care between 1994 and 2008 has been partially attributed to more specific diagnoses.[16]

LGS was defined by the International League Against Epilepsy (ILAE) in 1989,[17] and although the International Classification of Diseases, 10th Revision (ICD-10) was published in 1990, an International Classification of Disease code for LGS (G40.812) was not included until 2015.[11,18] Until sufficient time has passed to allow for the LGS code to become adopted,[11] healthcare databases not reliant on ICD-10 coding may provide the best source of data to investigate the prevalence and HCRU in LGS.

In the UK, a clinical terminology coding system (Read Codes) captures details within patients' electronic medical records (EMRs) of any primary and secondary care interactions, including records of patient symptoms, diagnosis, and prescriptions.[19] Since 2011, to ensure validity of the coded data, the ILAE has recommended that diagnoses of epilepsy are made by a healthcare professional with appropriate specialized training, and where diagnosis is definite, it should be recorded within primary care documentation.[20] However, while accurate identification of epilepsy is important for epidemiologic studies, it is not always possible and may result in errors in the coding process.[20] For this reason, the specificity and predictive value of diagnostic codes must be considered, and the ILAE further recommended that linked data should be validated in each population studied.

Use of the Read Code system for epilepsy diagnoses has been validated by several epidemiologic studies[16,21] and has demonstrated good sensitivity (86%) and specificity (97%).[21] A UK primary care database that has access to Read Codes is the Clinical Practice Research Datalink (CPRD).[19] As a Read Code for LGS has been available in the UK since 2009, the use of this database may permit a better understanding of HCRU in LGS. This is particularly true given that the primary care data can be linked to a range of other health-related data, including Hospital Episode Statistics (HES) and the mortality registry from the Office for National Statistics (ONS).[22,23] Until now, no study has investigated the prevalence of HCRU in LGS using the Read Code system, and studies have relied on secondary methods that utilize algorithms (based on epilepsy diagnosis and antiseizure medication [ASM] usage from claims data) to identify patients with probable LGS.[11,13] While useful, these studies have limitations as it is likely that not all patients will be prescribed the ASM in the algorithm. The objective of this retrospective cohort study was to use linked CPRD data to examine prevalence, demography, ASM usage, HCRU, and mortality of patients with LGS identified from the CPRD and HES databases, with additional data from the ONS.

Methods

Data source – CPRD

CPRD is a real-world database providing a quality-assured and validated source of longitudinal and representative UK population health data for epidemiologic and HCRU research.[22] Coded and anonymized patient EMRs are provided to the CPRD by a UK-wide network of more than 1700 primary care practices that have routinely collected data since 1987.[19,22] Patients with a known diagnosis of LGS or epilepsy that predated the introduction of CPRD could have their diagnosis entered into the system at or after its introduction. Thus, patients with an epilepsy diagnosis in CPRD could have been diagnosed before 1987. The present study used CPRD GOLD data, which includes EMRs contributed to CPRD using the Vision® GP IT software.[24] Using this software and recording information with coding systems such as version 2 Read Codes,[22] EMR data (patient demographics, diagnoses and symptoms, prescriptions, laboratory tests, and referrals to hospital and specialist care) are recorded by the GP against a patient's unique National Health Service (NHS) number,[22] which is available for 99.8% of primary care records.[25] In the present study, using the latest build of CPRD GOLD (11/03/2019), 13.7 million de-identified patient EMRs were used following collection from 01/01/1987–28/02/2019.

Data source – HES and ONS

For consenting patients and practices, linkages between CPRD GOLD and other health-related data (eg HES/ONS) were conducted via a third party (NHS Digital)[19] using patients' unique NHS numbers. As NHS numbers were introduced in 1996/7, linked data are not available for all patients registered in CPRD, resulting in fewer patients and a restricted period for HES linked and ONS linked data.[19] HES data include records of all admissions or attendances at participating NHS hospitals, records of patient care, type of outpatient consultation, specialists seen, clinical diagnoses, and procedures performed.[19] A&E visits are only reported in HES if they result in a subsequent hospital admission.[26]

Patient population

From this cohort, patients enrolled between 01/01/1987 and 31/10/2018 were included. Patients were defined with confirmed LGS if their EMR contained a Read Code for LGS (CPRD GOLD; code F250500). Patients with probable LGS were defined as those with an EMR containing an ICD-10 code/Read Code for epilepsy (from HES/CPRD) and a formulary product code for rufinamide within a year of diagnosis. Prescription of rufinamide was deemed the best indicator of LGS in patients with epilepsy, owing to its specific indication in patients with LGS[27] and use in previous claims database studies to identify probable LGS.[11,13] Patients with a prescription of stiripentol or potassium bromide were excluded to prevent inclusion of patients with probable Dravet syndrome. Regardless of the length of a patient's EMR, all patients with a record of LGS in the CPRD were included for analyses of prevalence. The index date for confirmed or probable LGS reflected the date of the last visit to a neurologist/pediatrician in the year preceding the first CPRD record of the epilepsy diagnosis.

Outcomes

The primary outcome was period prevalence of LGS. As many patients with LGS may have incomplete records, accurately identifying

the date of diagnosis and determining incidence is challenging. Also, considering the potential impact of mortality, prevalence was considered the preferred measure of determining the magnitude of LGS in the population that may result in HCRU.

Period prevalence of LGS was calculated for the last full calendar year of data from CPRD: 2017. Period prevalence was calculated using the number of confirmed/probable cases identified from CPRD GOLD and/or HES in 2017 (new and pre-existing) divided by the total number of patients within CPRD GOLD in 2017 (both in terms of units of person - time) and expressed as cases per 10,000 people. Patients who were deceased in 2017 were excluded from the calculations of prevalence.

Secondary outcomes included ASM usage (proportion of patients with ASM prescriptions during the follow-up period), HCRU (primary and secondary care - related visits/entries), and mortality reported over the follow-up period. For confirmed LGS, HCRU was estimated (per patient-year) after the date of LGS diagnosis; for probable LGS, the period from index date was utilized to estimate HCRU. As the availability of NHS numbers restricted linkage to a shorter period, HES and ONS linked data were available for a follow-up period of 01/04/1997–31/12/2017 and 02/01/1998–13/02/2018, respectively. Unlike the analyses to estimate period prevalence, patients who died during the follow-up period were included in calculations of ASM prescriptions and HCRU.

Primary care data (CPRD) were used to calculate ASM prescriptions, the number of consultations, and visits or telephone calls with GPs or nurses. For patients with HES-linked CPRD data, hospital inpatient admissions (number and duration [with a single consultant]), hospital outpatient visits, and A&E admissions were calculated. Hospital visits could have a maximum of 20 diagnoses and 24 procedures recorded against the visit and were not specifically epilepsy related, thus reflecting total HCRU.

Mortality rates were calculated for those patients with ONS linked data as the rate per 1000 person-years of follow up.

Baseline characteristics included age at diagnosis of epilepsy or LGS, follow-up duration, and sex. All available medical history was extracted for each patient identified, including demographic (sex and age at diagnosis) and clinical data (diagnoses, symptoms, prescription medication).

Data analyses

Two-tailed Student's t-tests ($p < 0.05$) were used to determine statistical differences, for baseline characteristics and outcomes, between patients with confirmed or probable LGS. To determine if there was a significant relationship between the age of patients in 2017 and the prevalence of LGS in the full cohort, a Chi-square test was used. In addition to stratification of outcomes by confirmed and probable LGS, prevalence was stratified by age group in 2017 (0–5, 6–11, 12–17, and ≥18 years), HCRU was stratified by age group at follow up (<12 years and ≥12 years), and inpatient admissions were stratified according to the presence of an epilepsy-related ICD-10 code (codes starting with G40) as the primary admission diagnosis.

Ethics and guidelines

CPRD has ethics approval from the UK's Health Research Authority (HRA) Research Ethics Committee to provide primary care and linked data for observational research.[22,23] An Independent Scientific Advisory Committee provided approval of the study (Reference number:18_236R). The guidelines for Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) were followed.[28]

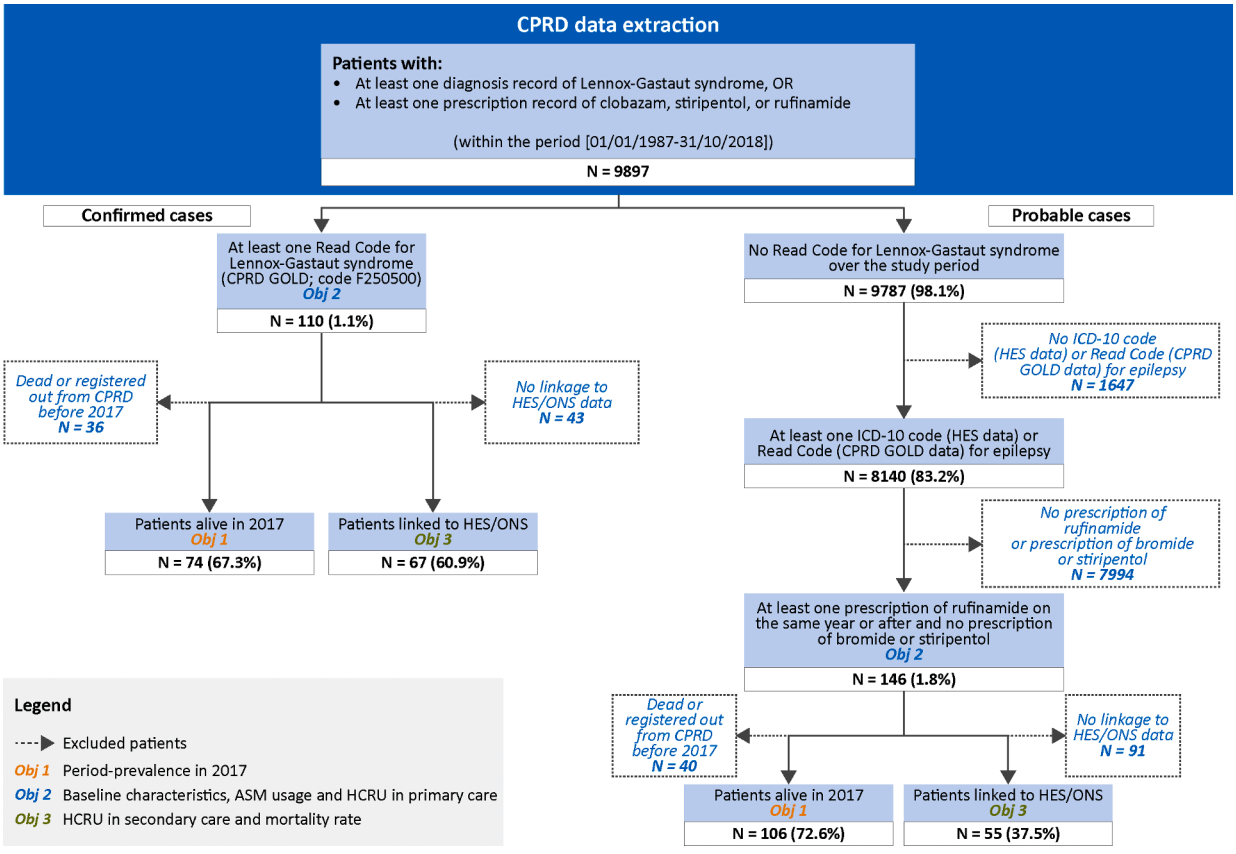

Figure 1. Overview of population by study objective
ASM, antiseizure medication; CPRD, Clinical Practice Research Datalink; HCRU, healthcare resource utilization; HES, Hospital Episode Statistics; ICD-10, International Classification of Diseases, 10th Revision; LGS, Lennox-Gastaut syndrome; ONS, Office for National Statistics.

Table 1
Baseline characteristics and length of follow up of patients with LGS

	Confirmed LGS[a] (n = 110)		Probable LGS[b] (n = 146)	Full cohort (confirmed + probable LGS; n = 256)	p-value
Age at diagnosis of LGS, yea					
Mean (SD)	13.8 (12.3)		NA	NA	NA
Median	10		NA	NA	
Min; Max	0; 61		NA	NA	
Age at index date (epilepsy diagnosis), years					
Mean (SD)	7.0 (10.0)		8.9 (11.0)	8.1 (10.6)	0.14[c]
Median	3.5		4	4	
Min; Max	0; 61		0; 54	0; 61	
Follow-up duration after index, years					
Mean (SD)	11.4 (8.6)	11.9 (7.8)		11.7 (8.2)	0.66
Median	9.5	9.7		9.6	
Min; Max	0.2; 32.2	0.6; 32.2		0.2; 32.2	
Sex, number (%)					
Male	72 (65)	81 (55)		153 (60%)	0.12[d]
Female	38 (35)	65 (45)		103 (40%)	

Abbreviations: ICD-10, International Classification of Diseases, 10th Revision; LGS, Lennox-Gastaut syndrome; NA, not applicable; SD, standard deviation. [a]Diagnosis confirmed by the Read Code for LGS: F250500. [b]LGS considered probable based on ICD-10/Read Code for epilepsy and at least one prescription of rufinamide within a year of diagnosis. [c]Two-tailed Student's t-test of confirmed versus probable cohorts. [d]Chi-square test of confirmed versus probable cohorts.

Results

Baseline characteristics

A total of 256 patients were identified with confirmed (110; 43%) or probable (146; 57%) LGS (Figure 1).

Baseline characteristics are presented in Table 1. For those with confirmed LGS, mean (SD) age at diagnosis of LGS was 13.8 (12.3) years, whereas the age at diagnosis of epilepsy was 7.0 (10.0) years. Patients with probable LGS had a similar age at epilepsy diagnosis to those with confirmed LGS (8.9 [11.0] years, p = 0.14).

Similar proportions of patients with confirmed LGS (66%) or probable LGS (56%) were male (p = 0.12) and follow-up duration, from epilepsy index date, was similar in both groups (confirmed: 11.4 [8.6] years; probable 11.9 [7.8] years, p = 0.66).

Prevalence

Extracted data from CPRD GOLD for those alive in 2017 constituted EMRs from 2,847,249 patients. Of the 256 patients identified in the full (confirmed + probable) cohort, 76 had died prior to 2017, leaving 180 patients (74 confirmed) alive for calculation of period prevalence (Figure 1 **and** Table 2). In general, period prevalence increased with age in the 0–17 years age group; however, a greater proportion of patients with probable LGS were in the 6–11 years group and a greater proportion of patients with confirmed LGS were in the ≥18 years group. These differences resulted in a significant dependence (p = 0.044) between age in 2017 and prevalence between the confirmed and probable LGS cohorts.

Comparing the index date for epilepsy in those with confirmed or probable LGS, cases increased steadily from 1959 and reached a peak for both groups in 2003–4 (confirmed LGS, n = 12; probable LGS, n = 15; Figure 2); after which, cases plateaued and fell in recent years. Before the introduction of a Read Code for LGS in 2009, 93 patients with confirmed LGS were diagnosed with epilepsy (85%) (Figure 2); of those, 70 had a Read Code for LGS in the same period (75%).

ASM usage

A total of 20 different ASMs were used by at least 10% of the confirmed and probable LGS cohorts during the follow-up period (Figure 3). ASMs used by at least half of those with confirmed LGS during follow up were (high to low, % of patients): valproate (72%), lamotrigine (69%), clobazam (66%), midazolam (64%), levetiracetam (55%), and diazepam (54%). Of note, rufinamide was used by 27% of those with confirmed LGS. With the exception of rufinamide, ASM usage in probable LGS was similar for the ASMs listed for confirmed LGS. In addition, several less commonly used ASMs were prescribed more widely for those with probable versus confirmed LGS, eg carbamazepine (46 vs 29%), oxcarbazepine (19 vs 6%), and pregabalin (14 vs 4%). During follow up, the mean (SD) number of ASMs used by a patient with confirmed LGS was 6.7 (3.4), and only a small minority (3.7%) of patients were prescribed only one ASM during this period. Similar data were found in the probable cohort with 8.5 (3.5) ASMs used during follow up.

Table 2
Period prevalence of LGS from UK CPRD by identification criteria and age group in 2017

	Confirmed LGS[a] (n = 74)	Probable[b] LGS (n = 106)	Full cohort (Confirmed + probable LGS; n = 180)	p-value
Prevalence, per 10,000 people				
Standardized to UK CPRD population	0.289	0.420	0.578	
Age distribution, n (prevalence per 10,000 people)				
0-5 years	2 (0.098)	6 (0.325)	8 (0.340)	0.044[c]
6-11 years	5 (0.327)	19 (1.221)	24 (1.134)	
12-17 years	13 (0.745)	13 (0.773)	26 (1.115)	
≥18 years	54 (0.264)	68 (0.336)	122 (0.496)	

Abbreviations: CPRD, Clinical Practice Research Datalink; ICD-10, International Classification of Diseases, 10th Revision; LGS, Lennox-Gastaut syndrome. [a]Diagnosis confirmed by the Read Code for LGS: F250500. [b]LGS considered probable based on the ICD-10/Read Code for epilepsy and at least one prescription of rufinamide within a year of diagnosis. [c]Chi-square test of prevalence.

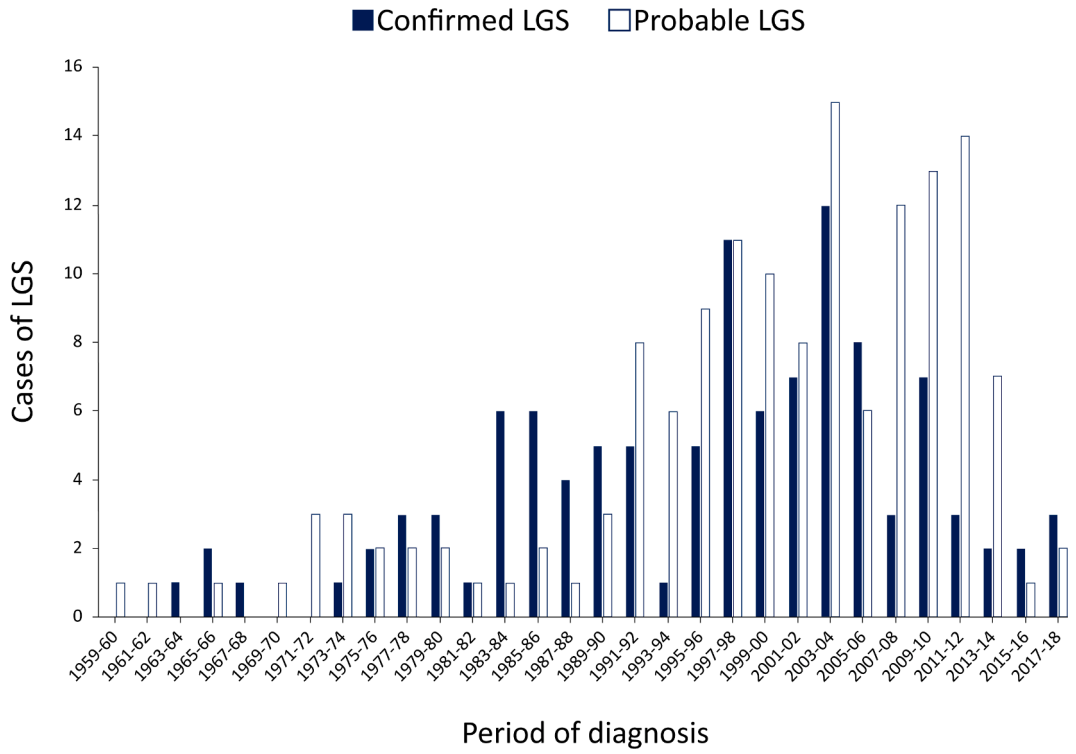

Figure 2. Period of epilepsy diagnoses in those with confirmed or probable LGS
ICD-10, International Classification of Diseases, 10th Revision; LGS, Lennox-Gastaut syndrome. Period of diagnosis based on the timing of the ICD-10/Read Code for epilepsy prior to prescription of rufinamide.

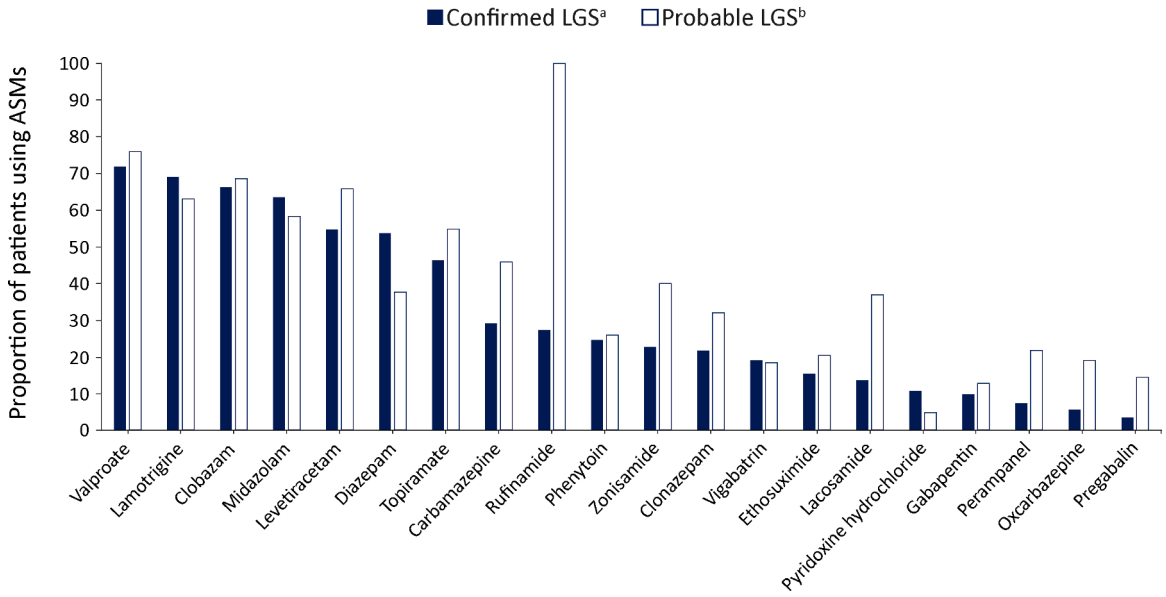

Figure 3. ASM usage during the follow-up period
ASM, antiseizure medication; ICD-10, International Classification of Diseases, 10th Revision; LGS, Lennox-Gastaut syndrome. [a]Diagnosis confirmed by the Read Code for LGS: F250500. [b]LGS considered probable based on the ICD-10/Read Code for epilepsy and at least one prescription of rufinamide within a year of diagnosis.

The mean (SD) number of ASMs used each year for those with confirmed LGS was 1.06 (0.27) and 1.12 (0.39) during 2010–13 and 2014–17; no patients used more than two ASMs (min; max of 0.25; 1.5 and 0.25; 2.00). Similarly, for those with probable LGS, there was a tendency for only one ASM to be used per year: 1.06 (0.27) and 1.22 (0.48) during 2010–13 and 2014–17; however, the upper range was increased to approximately three ASMs (min; max of 0.25; 1.5 and 0.25; 3.25).

Healthcare resource utilization

GP consultation was the most common contact method in primary care, followed by GP phone calls and nurse consultations; GP visits were rare, as were nurse visits or phone calls (Table 3**A**). Primary care HCRU was similar for confirmed LGS and probable LGS, with no significant difference found between the two groups irrespective of age at the time of HCRU. In secondary care, outpatient visits were the most common type of

Table 3
Healthcare resource utilization by identification criteria[a,b] and age group during follow up[c]

(A) Primary care	Confirmed LGS[a] <12 years (n = 39)	Confirmed LGS[a] ≥12 years (n = 89)	Probable LGS[b] <12 years (n = 71)	Probable LGS[b] ≥12 years (n = 115)	p-value[d] <12 years	p-value[d] ≥12 years
Number of primary care consultations, PPY						
All (nurse/GP)	6.46 (4.82)	6.79 (7.19)	7.75 (5.37)	7.99 (7.08)	0.22	0.23
GP consultations	4.95 (4.15)	3.94 (4.96)	5.54 (4.32)	5.97 (6.09)		
GP home visits	0.21 (0.57)	0.76 (2.66)	0.27 (0.56)	0.29 (0.78)		
GP phone call	0.69 (0.83)	1.03 (2.94)	0.83 (1.46)	0.54 (0.93)		
Nurse consultations	0.56 (1.12)	0.82 (1.13)	0.66 (1.16)	0.96 (1.18)		
Nurse home visits	0	0.06 (0.28)	0.03 (0.17)	0.06 (0.27)		
Nurse phone call	0.10 (0.38)	0.01 (0.11)	0.24 (1.43)	0.02 (0.13)		
(A) Primary care (B) Secondary care	Confirmed LGS[a] Confirmed LGS[a] <12 years (n = 20)	 ≥12 years (n = 55)	Probable LGS[b] Probable LGS[b] <12 years (n = 23)	 ≥12 years (n = 47)	p-value[d] p-value[d] <12 years	 ≥12 years
Number of hospital outpatient visits, PPY						
All causes	7.45 (9.51)	5.36 (7.61)	10.04 (10.49)	7.13 (7.48)	0.40	0.24
Number of hospital inpatient admissions, PPY						
All causes	1.65 (1.63)	1.09 (1.86)	3.61 (4.85)	1.26 (2.06)	0.093	0.67
Epilepsy related	1.50 (1.47)	0.96 (1.78)	3.04 (4.43)	0.89 (1.37)	0.14	0.83
Hospital inpatient LOS, days						
	(n = 129)	(n = 544)	(n = 575)	(n = 512)		
All causes	2.41 (5.87)	3.42 (8.53)	3.53 (11.06)	4.74 (11.94)	0.11	0.041
	(n = 120)	(n = 458)	(n = 473)	(n = 353)		
Epilepsy related	2.48 (6.07)	3.24 (6.80)	3.69 (11.98)	5.70 (13.90)	0.12	0.002
Number of A&E visits, PPY						
All causes	0.85 (1.18)	1.15 (2.17)	0.96 (1.69)	1.04 (2.54)	0.81	0.83

Data are mean (SD). Abbreviations: GP, general practitioner; ICD-10, International Classification of Diseases, 10th Revision; LGS, Lennox-Gastaut syndrome; LOS, length of stay; PPY, per patient-year; SD, standard deviation. [a]Diagnosis confirmed by the Read Code for LGS: F250500. [b]LGS considered probable based on the ICD-10/Read Code for epilepsy and at least one prescription of rufinamide within a year of diagnosis. [c]Data are shown by age at resource utilization, resulting in some patients being included in both groups. [d]Two-tailed Student's t-tests comparing HCRU between confirmed and probable LGS.

HCRU, followed by inpatient admissions and A&E visits (**Table 3B**). As with primary care consultations, for either age group and whether or not inpatient admissions were related to epilepsy, HCRU was generally similar when comparing confirmed with probable LGS. The exception was that the length of stay of inpatient admissions was significantly longer for probable versus confirmed LGS in the ≥12 years age group (all causes, p = 0.041; epilepsy related, p = 0.002).

Mortality

Considering only deaths identified in patients with CPRD linkage to ONS, 18 of 122 patients died over the follow-up period (confirmed: n = 11; probable: n = 7). Median age at death (min; max) for confirmed LGS was 26 (11; 46) and 16 (4; 64) years in probable LGS. Crude mortality rates of 6.12 (confirmed LGS) and 4.17 (probable LGS) deaths per 1000 person-years were calculated over a follow-up period consisting of 1796 and 1679 patient-years.

Discussion

To our knowledge, this is the first study to use large-scale and routinely collected UK healthcare data to identify patients with confirmed LGS and assess their HCRU. This study confirms a minimum prevalence of 0.289 per 10,000 people, multiple prescribed ASMs, high HCRU, and a high mortality rate in patients with LGS. Similar findings were found in patients with probable LGS, identified based on diagnosis of epilepsy and prescription of rufinamide, thus supporting the validity and specificity of this algorithm-based approach. Based on the prevalence of confirmed and probable LGS, we find a total prevalence of 0.578 per 10,000 people for LGS in the UK.

CPRD is a large representative and validated source of UK healthcare data[22] that allows linkage between primary care data (CPRD), secondary care data (HES), and general population mortality data (ONS).[23] Using this approach and the availability of a Read Code for LGS, we identified 110 patients with confirmed LGS and a further 146 patients with probable LGS, resulting in a large cohort of patients for analyses. Compared with previous studies in the USA and Finland, the prevalence of LGS in the UK CPRD was an order of magnitude lower than reported elsewhere (2.6–2.8 per 10,000 people).[9,10] The reasons for this low prevalence in the UK may reflect a multitude of issues, including the possibility that our studied population is somehow intrinsically different than previously studied populations, potential underdiagnosis, miscoding of LGS (for the confirmed LGS cohort), and lack of sensitivity of the Read Code system for identifying LGS especially prior to the introduction of an LGS code in 2009.

Although seemingly rare in this study, misdiagnosis may be attributable to the manual nature of data entry from secondary care, thereby resulting in incomplete or inaccessible data.[22] This would be consistent with why other studies from CPRD similarly find a lack of specificity with epilepsy coding.[29] Patient-identifiable data (eg letters or free text entries) may be omitted from EMRs owing to data governance reasons[22,24] and a lack of GP incentives to be more exact with the coding of data taken from secondary care.[16] While this may explain some of the patients that we may have missed in our minimum estimate of the period prevalence of LGS, it is clear a sizeable proportion of patients do have their records retrospectively updated with the appropriate Read Code data (for example, 75% of patients with an epilepsy diagnosis prior to 2009 also had a Read Code for LGS in this period).

The probable LGS cohort in this study attempted to overcome these challenges of misdiagnosis and miscoding. However, the combined prevalence of confirmed and probable cases was still lower than previously reported.[9,10] We took a conservative approach of using prescription of rufinamide, an ASM specifically indicated for LGS[27], as a marker for probable LGS; only 27% of patients with confirmed LGS used rufinamide. The low use of rufinamide in confirmed LGS might result from the fact that much of the available CPRD data predate the license date of rufinamide in Europe (2007).[27] Further, our data reflect the evolution of LGS diagnosis from epilepsy to the specific epilepsy syndrome of LGS;[14] epilepsy was diagnosed on average 6.8 years before LGS. In some cases, the patient's index date for confirmed LGS (data not shown) predated the introduction of the Read Code in 2009, suggesting some GPs retrospectively changed the coding for their patients. This retrospective

coding is also supported by the finding that the pediatric syndrome of LGS was coded in patients aged up to a maximum of 61 years. Therefore, some patients with LGS were not managed according to specific LGS guidelines and may have been missed from the probable LGS cohort because rufinamide was not prescribed. While this might be anticipated to result in differences between the two cohorts, these were generally only subtle and not statistically significant.

In general, ASM usage and HCRU in primary and secondary care were similar in confirmed and probable LGS. ASM usage aligned with established guidelines for the treatment of LGS, with most using no more than two or three ASMs at one time (most often being valproate and lamotrigine).[14,30] These findings support the conclusion that despite the probable cohort lacking an LGS Read Code, these patients had a disease more characteristic of treatment-resistant epilepsy, likely resulting from LGS. Since treatment resistance is much more common in LGS (76–97% of adults[31,32]) than in epilepsy (23–26%[29,33]), it can be expected to result in a greater number and diversity of ASMs over the long term. In the present study, 7–8 ASMs were used in those with probable or confirmed LGS (during a follow-up period of 8–12 years); this is similar to other long-term studies of LGS[13,34] and higher than that reported in patients with epilepsy where monotherapy is more common than polytherapy.[33]

In addition to ASM usage, HCRU was also similar to previous algorithm-based LGS studies. In a US-based retrospective claims study, physician visits (≥8 per patient-year; PPY), inpatient admissions (~1 PPY), outpatient (>5 PPY), and emergency visits (~1 PPY)[11] were similar to those from the present study in the older age group with LGS. For secondary care, this HCRU is more frequent in the LGS population from CPRD than the general population in the UK (inpatient admissions ~0.4 PPY, outpatient ~1.5 PPY, and emergency visits <0.2 PPY).[26]

Although significantly higher HCRU and costs have been demonstrated with LGS versus the general population, a similarly designed US study using patients with epilepsy as the control group found contrasting results.[13] In the study by Piña-Garza et al. (2017), the number of hospital visits was similar in the LGS and epilepsy populations; however, costs remained significantly higher with LGS owing to differences in medical costs over the ~10-year observation period.[13] While the present study has no control group, a previous study in the UK, using The Health Improvement Network (THIN) database, reported lower ASM usage (mean <2 ASMs) and HCRU (<1 visit PPY) in patients with epilepsy[12] than found here for LGS. Taken together, these studies indicate that the findings from CPRD are consistent with the hypothesis that both confirmed and probable LGS populations utilize significantly more healthcare resources. Subsequently, they are more likely to contribute to higher costs than the general public or populations with less severe epilepsy. Future studies are required to investigate this further.

Mortality in patients with LGS has been reported to be ~13–15 times higher than the general population, depending on the presence or absence of infantile spasms.[35] Results from the present study, using ONS linked data, demonstrate patients with LGS have a crude mortality rate of 4–6 per 1000 person-years (over a follow up consisting of ~1700–1800 patient-years) that is higher than that reported for the general population in England (0.6 per 1000 person-years)[36] and the overall epilepsy population in the UK (0.9 per 1000 person-years)[12] but comparable to the epilepsy population with at least one seizure per day (4.9 per 1000 person-years).[12]

Some of the study's limitations have been described above, particularly the limitations of coding and prescription of rufinamide in the definition of probable LGS. It may be argued that inclusion of additional ASMs or an age cut-off for diagnoses (eg less than 8 years) could have been used; however, such approaches would have compromised the specificity and sensitivity of the algorithm. While CPRD is representative of the UK population, non-primary care data are not fully captured or may be inaccessible. We could not access patient-level diagnostic data (eg electroencephalogram and imaging), which limited our ability to confirm LGS diagnoses in primary care by any other means. In addition, the high proportion of retrospective coding of LGS may have contributed to inaccuracies in the index date for LGS. Additional limitations include the absence of a direct reference population and the absence of other HCRU data (eg allied health professional visits), which limits the study's ability to capture the total burden of LGS illness to the healthcare system.

Conclusion

Our findings suggest that the prevalence of LGS in the UK is lower than previously reported, with our results being a minimum estimate. While our findings provide valuable information on the burden of illness of LGS, they are likely an underestimate. Future UK-based epidemiological studies, reliant on changeable Read Code data, should consider the potential of the Read Code system to underestimate the prevalence of specific epilepsy syndromes. The algorithm utilized in the current study was highly specific for LGS as the confirmed and probable cases had similarly high ASM usage, HCRU, and mortality rates, all of which are similar to previously published data. However, the algorithm may be poorly sensitive for LGS given the low prevalence observed compared with other studies, although other possible explanations cannot be ruled out. Our findings highlight the complex nature and high burden of LGS management in primary and secondary care settings.

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Data statement

Data were obtained from CPRD after going through their process for obtaining access, which includes ethics approval. The data were analysed by Syneos on behalf of GW Pharma Ltd to answer this particular research question. While the same data cut could be obtained from CPRD, the current data are confidential.

Disclosure of conflicts of interest

RC has received consultancy fees from Eisai, GW Pharmaceuticals companies, and Zogenix. He has been a principal investigator for GW Research Ltd and is a shareholder in Rize Medical Cannabis and Live Sciences UCITS ETF. FG is an employee of Syneos Health. MM was an employee of Syneos Health at the time of study completion. RH is employed by GW Pharma Ltd, London, UK. OP has received consultancy fees from GW Pharmaceuticals companies and Arvelle therapeutics.

All authors met the ICMJE authorship criteria and had full access to relevant data. Neither honoraria nor payments were made for authorship.

Author contributions

All authors contributed to the study concept, design, and interpretation of the data. FG analysed the data.

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