Received: 29 September 2023 | Revised: 12 February 2024 | Accepted: 12 February 2024

DOI: 10.1111/epi.17932

Epilepsia®

CRITICAL REVIEW

A comprehensive systematic literature review of the burden of illness of Lennox–Gastaut syndrome on patients, caregivers, and society

J. Helen Cross[1] | Arturo Benítez[2] | Jeannine Roth[3] | J. Scott Andrews[2] | Drishti Shah[2] | Emma Butcher[4] | Aimee Jones[4] | Joseph Sullivan[5]

[1]University College London National Institute for Health and Care Research Biomedical Research Centre Great Ormond Street Institute of Child Health, London, UK

[2]Takeda Pharmaceutical Company, Cambridge, Massachusetts, USA

[3]Takeda Pharmaceuticals International, Zurich, Switzerland

[4]Oxford PharmaGenesis, Oxford, UK

[5]Department of Neurology, University of California, San Francisco, San Francisco, California, USA

Correspondence
Joseph Sullivan, Department of Neurology, University of California, San Francisco, San Francisco, California, USA.
Email: joseph.sullivan@ucsf.edu

Funding information
Takeda Pharmaceutical Company

Abstract

Fully elucidating the burden that Lennox–Gastaut syndrome (LGS) places on individuals with the disease and their caregivers is critical to improving outcomes and quality of life (QoL). This systematic literature review evaluated the global burden of illness of LGS, including clinical symptom burden, care requirements, QoL, comorbidities, caregiver burden, economic burden, and treatment burden (PROSPERO ID: CRD42022317413). MEDLINE, Embase, and the Cochrane Library were searched for articles that met predetermined criteria. After screening 1442 deduplicated articles and supplementary manual searches, 113 articles were included for review. A high clinical symptom burden of LGS was identified, with high seizure frequency and nonseizure symptoms (including developmental delay and intellectual disability) leading to low QoL and substantial care requirements for individuals with LGS, with the latter including daily function assistance for mobility, eating, and toileting. Multiple comorbidities were identified, with intellectual disorders having the highest prevalence. Although based on few studies, a high caregiver burden was also identified, which was associated with physical problems (including fatigue and sleep disturbances), social isolation, poor mental health, and financial difficulties. Most economic analyses focused on the high direct costs of LGS, which arose predominantly from medically treated seizure events, inpatient costs, and medication requirements. Pharmacoresistance was common, and many individuals required polytherapy and treatment changes over time. Few studies focused on the humanistic burden. Quality concerns were noted for sample representativeness, disease and outcome measures, and reporting clarity. In summary, a high burden of LGS on individuals, caregivers, and health care systems was identified, which may be alleviated by reducing the clinical symptom burden. These findings highlight the need for a greater understanding of and better definitions for the broad spectrum of LGS symptoms and development of treatments to alleviate nonseizure symptoms.

Affiliations for Jeannine Roth and Emma Butcher were at the indicated institutions at the time the study was conducted.

KEYWORDS
caregiver burden, comorbidities, nonseizure symptoms, symptom burden

1 | INTRODUCTION

Lennox–Gastaut syndrome (LGS) is a rare developmental and epileptic encephalopathy[1] that is estimated to account for 1%–10% of childhood epilepsies[2] and is characterized by multiple drug-resistant seizure types, specific abnormal electroencephalogram showing bursts of slow spike–wave complexes and generalized paroxysmal fast activity, and intellectual and behavioral impairment.[3] Diagnosis of LGS is hindered by multiple factors, including the lack of disease biomarkers, and heterogeneous etiology and presentation.[4–6] Seizures associated with LGS are typically not controllable with antiseizure medications (ASMs), and drug resistance is common.[5,7] In addition to the multiple seizure types experienced by patients, LGS is also associated with a range of nonseizure symptoms, including intellectual disability, motor impairments, deficits in communication and sleep, and psychiatric and behavioral issues, for which there are also no effective treatments.[6] Although nonseizure symptoms are likely to contribute significantly to the burden of illness of LGS, there has thus far been no thorough analysis of their effects on patients, caregivers, and society. Although individual studies have identified negative physical, social, emotional, and financial impacts of LGS for individuals and their caregivers,[8–10] until now, only one systematic literature review (SLR) has evaluated the burden of illness of LGS.[11] Compared with single studies, SLRs are able to cover a broader range of subjects, enabling effective evaluation of all available evidence and easier identification of shortcomings or evidence gaps.

To gain a comprehensive understanding of the burden of illness of LGS, the present SLR evaluated data on clinical symptom burden, comorbidities, care requirements, quality of life (QoL), economic burden, caregiver burden, and treatment burden. The aim of the present SLR was to identify evidence gaps to guide further research and inform development of new interventions to improve the lives of patients and their caregivers.

Key points

- Reducing the high clinical symptom burden of LGS could increase quality of life of patients and caregivers
- LGS is associated with high direct costs due to health care resource use and medications; data on indirect costs are lacking
- Pharmacoresistance is common, and most individuals with LGS require polytherapy and changes to treatment over time
- There is an unmet need for treatments that address the nonseizure symptoms of LGS
- There is a need for a greater understanding of and better definitions for the broad spectrum of LGS symptoms

2 | MATERIALS AND METHODS

This SLR was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines and registered on PROSPERO (ID: CRD42022317413).[12]

2.1 | Objectives

The primary objective was to describe data on the burden of illness of LGS globally, across the domains of clinical symptom burden, comorbidities, care requirements, humanistic burden on individuals and caregivers, economic burden, and treatment burden. The secondary objective was to identify reasons for variations in findings across the included studies, and any current data gaps.

2.2 | Outcomes

The main outcomes were clinical symptom burden (types and patterns of seizure and nonseizure symptoms), prevalence of comorbidities, care requirements, humanistic burden on individuals and caregivers, economic burden, and treatment burden.

2.3 | Eligibility criteria

Noninterventional studies of any design were eligible for inclusion if they presented original research on one or more outcomes of interest and included primary or subgroup analyses in an LGS population (Table S1–S6). Inclusion was not restricted by population, country of origin, or publication date. Publications written in English

and non-English publications with an English abstract were considered for inclusion. Preclinical studies, case reports, reviews, and interventional studies in which individuals were actively assigned to a therapy were excluded. For this review, the use of screening, diagnostic tests, or assessments (including qualitative interviews) was not defined as intervention.

2.4 | Data sources

Relevant literature was identified via MEDLINE, Embase, and the Cochrane Library from inception to March 15, 2022. For the period 2017–2022, supplementary manual searches were also performed by one reviewer (E.B.) to identify relevant proceedings from key congresses, websites, and publications listed in bibliographies of review articles (Table S2).

2.5 | Search strategy

Two reviewers (A.J and E.B.) used a combination of Medical Subject Headings and free-text terms to identify relevant literature (Table S2). The results from MEDLINE, Embase, and Cochrane Library searches were downloaded via Endnote into a bespoke Microsoft Excel database. After deduplication, titles and abstracts, followed by full texts, were screened in duplicate by independent reviewers (E.B., A.J., and nonauthor reviewers). Discrepancies were resolved by reviewer discussion or escalation to a third independent reviewer (E.B., A.J., and nonauthor reviewers). Articles identified during supplementary manual searches were added to the final included list of publications after full-text screening.

2.6 | Data extraction and quality assessment

Data on the study design, population, and outcomes were extracted from publications by a single reviewer for each article. This reviewer also assessed study quality based on a series of "risk of bias" questions adapted from the Strengthening the Reporting of Observational Studies in Epidemiology statement,[13] the Appraisal Tool for Cross-Sectional Studies,[14] and the Newcastle–Ottawa quality assessment scales.[15] Risk of bias was rated as high, medium, or low across eight categories relating to study design, methodology, and reporting, to reflect potential concerns over the reliability and generalizability of the reported results. Seizure types were recorded exactly as they were described in each article, which included seizure type terminology that has since been discontinued.[16]

2.7 | Data synthesis

Owing to heterogeneity and the qualitative nature of some outcomes, no quantitative synthesis or subgroup analyses were performed. Results are presented as narrative and tabulated summaries, with descriptions of themes, variation, and quality concerns. Costs describing the economic burden were standardized to a single currency, when possible, accounting for or noting potential differences by year of publication, inflation, and other economic conditions.

3 | RESULTS

3.1 | General findings

After screening 1442 deduplicated records from databases and registers, 108 were eligible for inclusion in this review (Figure 1). Five additional articles were identified in the supplementary searches, leading to a total of 113 included articles (Figure 1). Most of the included studies reported on the clinical burden of seizure symptoms, treatment burden outcomes, or both (Figure 2). Conversely, there were few reports on caregiver burden or humanistic burden.

North America had the highest representation of studies ($n = 39$), followed by East Asia ($n = 32$) and Europe ($n = 31$) (Table S3). Other regions, including South America ($n = 9$), western Asia ($n = 7$), Oceania ($n = 3$), and Africa ($n = 2$), were poorly represented.

3.2 | Quality assessment findings

A summary of the qualitative assessment results is given in Table S4. Briefly, few quality issues were noted in terms of study design, methodology concerns, and clarity of reporting in the Results and Discussion sections. Quality concerns were noted for sample representativeness ($n = 95$), disease and outcome measures used ($n = 57$), and overall reporting clarity ($n = 39$). These concerns were raised owing to the inclusion of small or selective samples, a lack of clarity on or confirmation of LGS diagnosis, unclear selection criteria, and limited reporting clarity because of the type of publication (i.e., abstract). Although no studies were excluded owing to quality assessment findings, quality concerns were considered when analyzing the extracted data and reporting findings.

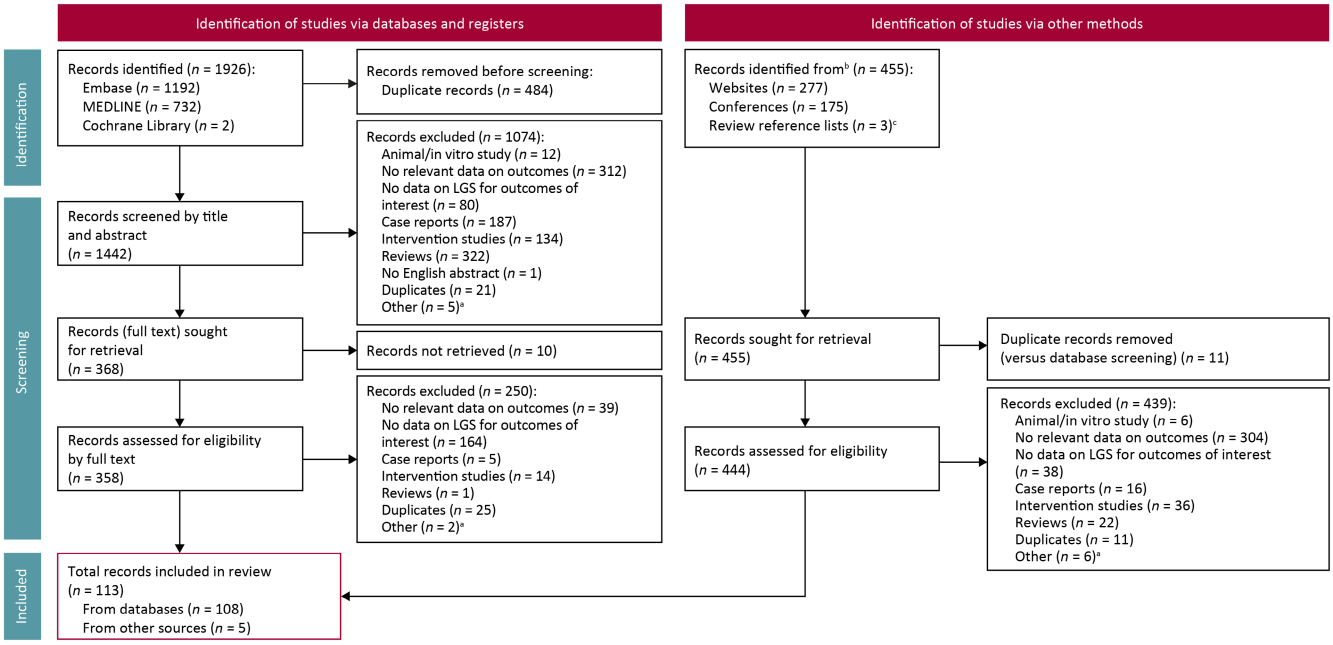

FIGURE 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram. [a]In the database search, at title and abstract screening, other reasons for exclusion were reporting of the same study or interim analysis of data in another record ($n=3$), and no abstract and judged to not be relevant based on title alone ($n=2$); at full-text screening, other reasons were interim analysis of data in another record ($n=2$); and in the manual search, other reasons were that full information was unavailable ($n=6$). [b]Records manually screened by a single reviewer. [c]Assessed reference lists of all reviews published between 2017 and 2022 and on relevant topics. LGS, Lennox–Gastaut syndrome.

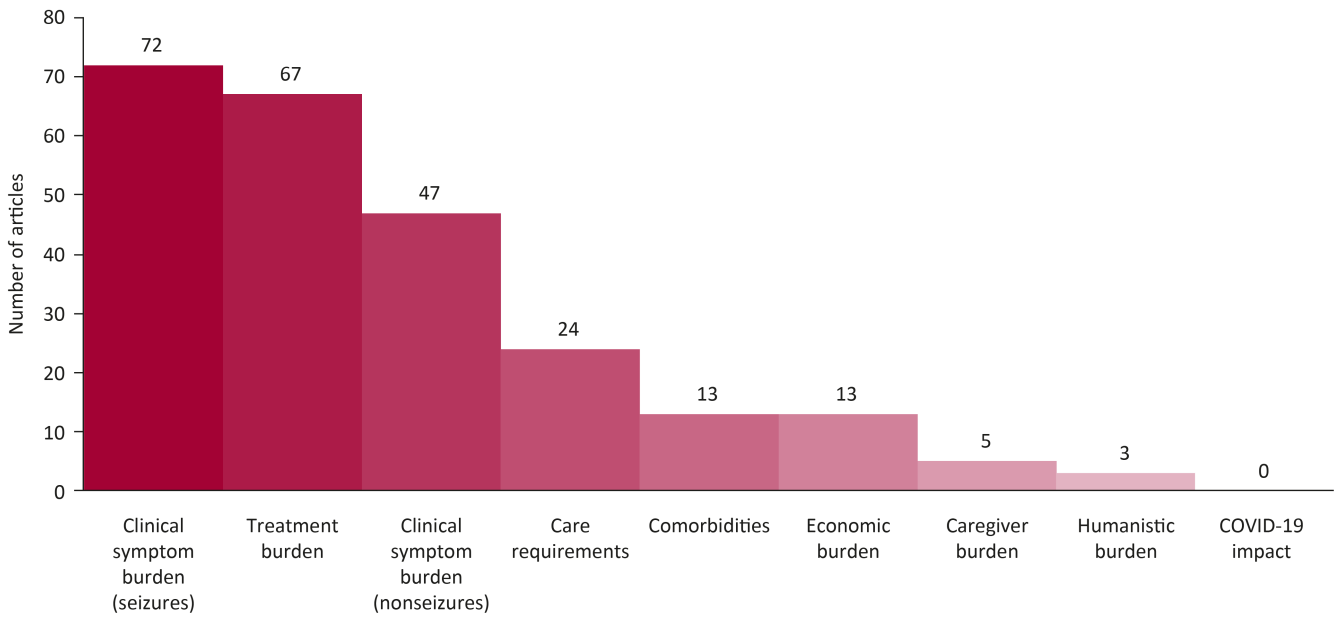

FIGURE 2 Number of studies reporting on the outcomes of interest. Studies could be in more than one category.

3.3 | Clinical symptom burden and comorbidities

3.3.1 | Seizures

Of the 72 studies reporting the burden of clinical seizure symptoms, six studies (two each in Asia, Europe, and North America) included the age at first seizure, which ranged from 1 month to >9 years. No clear differences by geographical location or publication date were apparent.[17–22] Studies including both children and adults ($n=3$) reported an average age at first seizure of 1–3 years,[20–22] which is older than that reported in the studies that included children only ($n=3$).[17–19] Across eight studies with

relevant data, 0%–60% of individuals with LGS experienced infantile spasms, either before the onset of epilepsy or as the first recorded seizure type.[19–26]

Data from 17 studies showed that individuals with LGS generally experience 2–4 concurrent seizure types, although substantial interindividual heterogeneity existed, with an overall range of 0–7 seizure types per individual.[20,21,26–40] Five studies reported the mean number of seizure types per individual, which was between 2.6 and 3.6.[28,37–40] These data were generally aligned with those from studies that reported the proportion of individuals experiencing different numbers of seizure types (Figure 3).[20,21,26–36] One study reported a high prevalence of individuals with one seizure type (38%); however, this study used historical records of seizure types experienced over 14 years.[29]

Four studies reported a decrease in the number of seizure types experienced per individual during the study, which may reflect changes with age.[20,27,34,41] Similarly, a decline in the prevalence of individual seizure types (tonic, tonic–clonic, myoclonic, and atypical absence) over time was reported in multiple studies (Table S5).[20,36,38,42,43] Three studies also noted reductions in the prevalence of atonic seizures over time.[20,36,43]

In all 11 studies that reported continuous measures of seizure frequency, individuals with LGS were found to experience more than one seizure per day.[29,30,37,41,44–50] Seizure frequency ranged widely within and across studies, which may be partly owing to interindividual heterogeneity; in one study, baseline seizure frequency was 15–3000 seizures per month.[46,51] These findings aligned with those from studies in which individuals were categorized by seizure frequency; 50%–100% of individuals were reported to have daily seizures, and those without daily seizures were usually reported to have seizures at least once per week.[18,20,23,26,28,34–36,52–58]

Several prospective and retrospective studies showed decreases in seizure frequency over time, reporting similar ranges of seizure freedom prevalence at last visit (9%–28% and 4%–28%, respectively).[17,20,34,38,43,47,59–67] Although the duration of data collection varied considerably between studies (3–20 years), no correlation between the change in seizure frequency and the duration of data collection was observed.[20,34,38,43,47,59–64] One study showed that 33.3% of children treated with clobazam had seizure-free status maintained for a period of 5.5 months, 25% of children treated with topiramate had seizure-free periods ranging from 8 months to

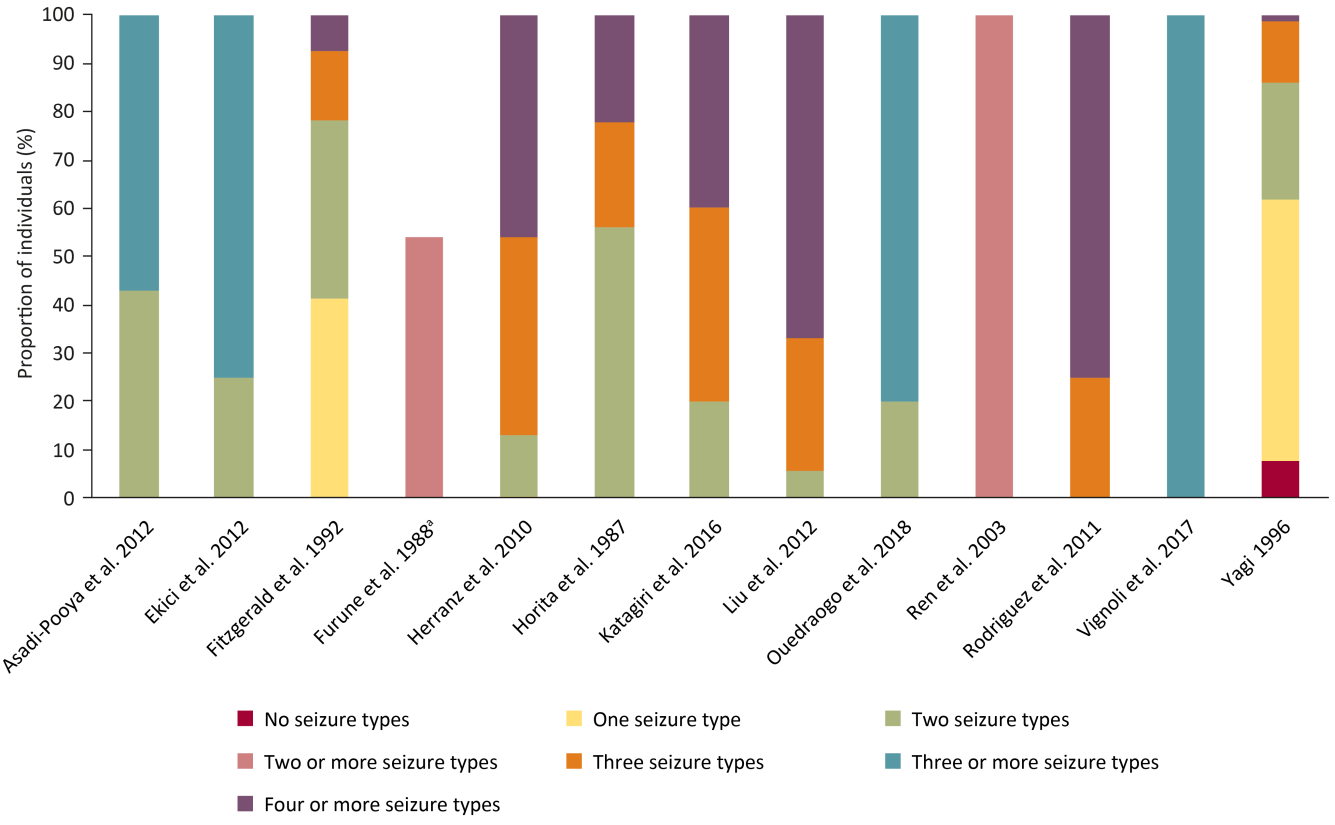

FIGURE 3 Number of seizure types experienced by individuals per study. For studies with a longitudinal design (Furune et al.,[20] Horita et al.,[31] Yagi[27]), the figure reflects data from the last available time point. The remaining studies only provided data at one time point. [a]Data were reported for only 54% of individuals.

2.5 years, and 11% of children treated with lamotrigine had seizure-free periods of 6 months.[26] In another study, 70.6% of children had at least one seizure-free period up to their fifth birthday, with a median longest seizure-free period of 13.5 months.[17]

The prevalence and frequency of seizure types observed in individuals with LGS are summarized in Table S5. Tonic seizures showed the highest prevalence of all reported seizure types, followed by tonic–clonic and myoclonic seizures. Several definitions were used for atonic, astatic (now referred to as atonic),[16] and absence seizures, and status epilepticus, precluding a clear conclusion on prevalence. Additionally, some studies reported the prevalence of drop attacks, which can encompass several seizure types, including atonic, tonic, and generalized tonic–clonic seizures.

3.3.2 | Nonseizure symptoms and comorbidities

Overall, 59 studies reported on nonseizure symptoms or comorbidities. In the present review, all data are combined and original study terminology (i.e., "nonseizure symptom" or "comorbidity") is used when relevant. Distinguishing between nonseizure symptoms and comorbidities was difficult given the overlapping definitions across studies, with 47 studies reporting on nonseizure symptoms (Table S6) and 12 studies reporting on comorbidities (Figure 4). Overall, the most common nonseizure symptoms or comorbidities were developmental delay, intellectual disability, and motor impairments.

Developmental delay was common in individuals with LGS, with eight studies reporting a prevalence of 79.6%–100% (Table S6). These delays were often severe or profound (>50% prevalence based on three articles)[21,25,68] and associated with developmental regression (44% prevalence based on one article).[65] Furthermore, based on 19 studies, at least 90% of individuals with LGS had intellectual disability, often of moderate to profound severity (reported by 14 articles to be present in at least 50% of the sample), and four studies noted that severity may worsen over time. Compared with studies in which it was described as a nonseizure symptom, the prevalence of intellectual disability when described as a comorbidity was more varied (59% and 100% in two studies).[33,69]

Eleven studies reported on motor impairments, which were frequent in individuals with LGS, with one study reporting difficulty walking in 81% of individuals.[70] However, variation in the measures and definitions used prevented definitive conclusions on the prevalence and severity of specific motor problems (e.g., motor handicap, walking/sitting) or symptoms (e.g., ataxia, hypotonia, paresis, spasticity).

Based on six studies, many individuals with LGS showed difficulties with communication, with up to 60% of individuals reported to have speech disorders (including dysarthria) and one study showing 60% of patients to be nonverbal.[21,26,29,68,70,71] In one study ($n = 24$ parents), 96% of parents reported that their child could not communicate appropriately for their age.[70] Two studies described comorbidities of language disorders, reporting a prevalence of 40% and 42%.[33,72]

Autism[33,36,58,60,69,73] and cerebral palsy[25,32,72–74] were comorbidities reported in six and five studies, respectively, with prevalence estimates of 6%–13% and 22%–33% of individuals, respectively (Figure 4). The prevalence estimate for autism excluded studies with unreliable estimates, namely one study with only five individuals[33] and another study in which "probable" LGS only was identified.[69] Although the latter study described patients with "probable" LGS and was excluded from the prevalence estimate for autism, the article did meet criteria for inclusion in the present review, because patients were identified from insurance claims records using a machine-learning model based on treatment- and diagnosis-related data. Identified patients were also reviewed by clinicians to ensure suitability for inclusion. In the present review, the estimate for cerebral palsy excluded studies with small or selective samples, namely a study of vagus nerve stimulation (VNS)[73] and another with a small sample size (23 individuals).[25] If included, these studies would change the range of prevalence estimates for autism and cerebral palsy to 0%–20% and 22%–56%, respectively.

Other symptoms were grouped into comorbidities defined as psychiatric and behavioral issues, and were reported in five studies[24,26,68,75,76]; however, methods and findings were heterogeneous, preventing any clear conclusions regarding prevalence. One study reported that 76% of individuals had behavioral issues[68]; another study found that 80% of individuals had hyperactivity, aggressiveness, and autistic features.[75] Conversely, other studies reported lower prevalence, potentially owing to their focus on specific symptoms (e.g., hyperactivity)[75] or behavioral syndromes (e.g., anxiety, attention-deficit/hyperactivity disorder, or psychosis).[76] Studies that described psychiatric and behavioral issues as comorbidities generally reported lower prevalence (35%–42%) than those that described them as nonseizure symptoms (35%–50%).[36,72,77]

Other problems included difficulty swallowing (reported in two studies)[43,70] and strabismus (reported in one study with a prevalence of 5.3%).[36] Based on five studies, individuals with LGS spent less time in sleep stage 2 and in rapid eye movement sleep than those without LGS.[31,68,78–80]

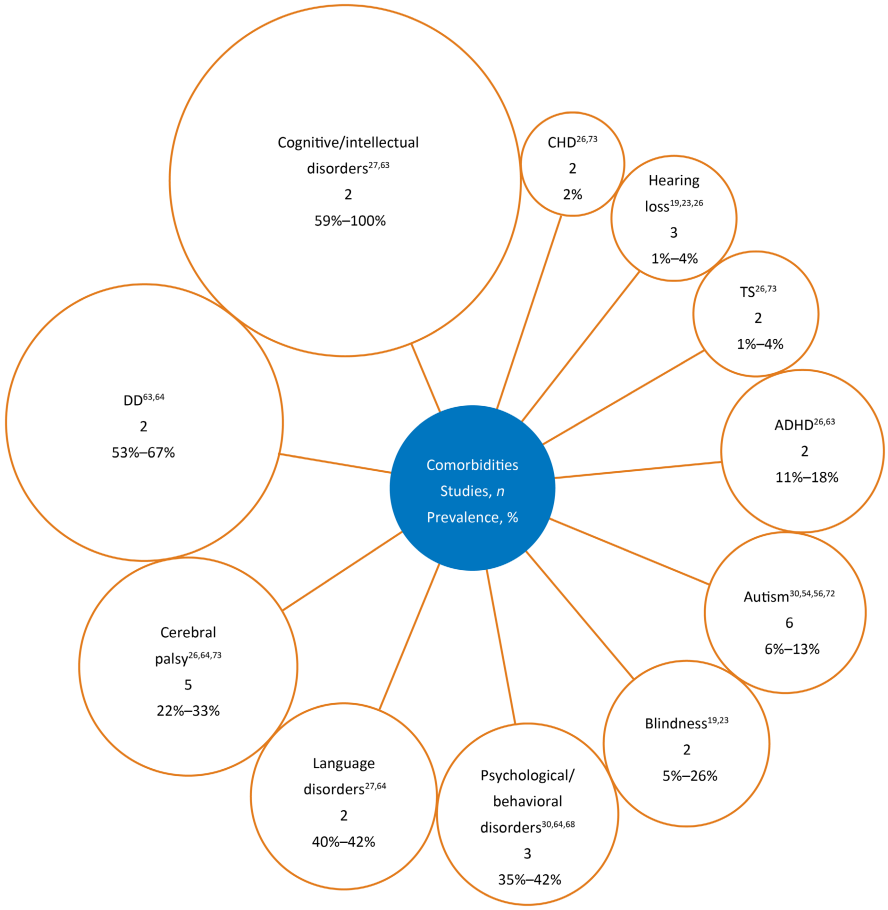

FIGURE 4 Prevalence of comorbidities. Comorbidities reported in only one study were excluded. ADHD, attention-deficit/hyperactivity disorder; CHD, congenital heart disease, DD, developmental delay; TS, tuberous sclerosis.

Prevalence estimates of comorbidities reported in only one study each were overweight/obesity (80%)[81]; acute upper respiratory tract infections (44%)[72]; bone fracture (31%)[69]; postviral encephalitis (6%)[74]; insomnia (5%)[36]; Down syndrome (4%)[74]; hypothyroidism (3%)[32]; myelomeningocele (2%)[74]; cancer (2%)[32]; diabetes, hypopituitarism, and renal failure (1% each)[32]; and urinary incontinence, osteoporosis, and gastrointestinal conditions (not specified).[36]

3.4 | Care requirements

Overall, 24 studies assessed the care requirements of individuals with LGS, which were found to be considerable owing to the high prevalence of seizure and nonseizure symptoms, as well as frequent comorbidity. In terms of daily assistance, 60.3% of adults ($n=41$) in one study lacked independent daily living skills, including bathing, eating, functional mobility, and toileting.[82] Thirteen studies reported that individuals with LGS frequently have problems with mobility and eating, including difficulty walking, lack of functional grasp strength, and a requirement for tube feeding (Table 1).[10,21,26,28,45,49,58,68–70,82–84]

The considerable clinical symptom burden associated with LGS means that individuals often require education outside of mainstream settings,[30,59] and few individuals complete high school (5.1% and 22.6% completion rate in two studies) or undertake higher level education (Table 1).[22,32,38] Additionally, many individuals cannot live independently or support themselves economically, often requiring full-time caregiver support in childhood and residential care in adulthood (Table 1).[27,30,36,38,42,45,49,77,85]

3.5 | Humanistic and caregiver burdens

Only three studies provided information on the QoL of individuals with LGS, with sample sizes ranging from 40 to 416.[9,68,86] Given the absence of validated scales for assessing the QoL of individuals with LGS, this outcome was not measured directly in any of the studies; instead, assessment was reliant on caregiver interviews or surveys. Moreover, no studies directly questioned individuals with LGS, probably owing to the intellectual disability associated with LGS. In one study, a conceptual model was developed to reflect four identified themes around the impact of LGS on QoL (physical, cognitive and behavioral, social,

TABLE 1 Care requirements identified for individuals with LGS.

Impact on daily living	
Mobility	• Many children with LGS are unable to walk or are unsteady and fall easily[10] • Approximately 45% of children can walk with support (e.g., assisted mobility devices)[58,83] • Up to 25% of individuals are unable to walk or are "bedridden"[21,26,28,58,82] • Wheelchair use was reported in 60%–73% of individuals; a lower prevalence of 5% was reported in only one study with a relatively small sample of 20 patients[26,45,49,68] • Protective equipment, including helmets and face guards (prevalence estimates up to 52.4% and 14.3%, respectively), is sometimes used to reduce risk of physical injury due to reduced mobility and seizures[10,45,49,69,84] • In one study, 11% of individuals did not have functional grasp strength[83]
Eating	• Considerable support or dependence for eating was reported in 54%–63% of individuals[70,83] • Tube feeding was used in approximately 30% of individuals (27%–38% across three studies), with a relatively large study in 416 caregivers reporting that 27% of individuals with LGS were tube-fed[50,68,70]
Other skills and functions	• Individuals with LGS are often unable to use speech and require considerable support to communicate[21] • In one study, toileting was reported as a care requirement for 80% of 36 children aged 3 years or older[83] • Respiratory help was reported as a care requirement in one study, which was limited to individuals with LGS or mitochondrial disease[50] • Very few individuals with LGS can drive[38,77]
Impact on schooling and living requirements	
Schooling	• One study in Spain reported that 62% of individuals were schooled at a special education center, and only 2% were placed in ordinary schools[30] • Literacy levels are low, with one study finding that 73.1% of adults are illiterate[38]
Living placement	• The highest prevalence of residential care was in a study in adults in France and Denmark ($n = 15/27$ [55.6%]); the remaining adults lived with family ($n = 12/27$ [44.4%])[42] • In studies that included both children and adults, 8%–24% of individuals in various countries were living in residential care[27,30,45,49,85]; 71%–89% lived with family[30,45]

Abbreviation: LGS, Lennox–Gastaut syndrome.

and treatment).[9] These themes were consistent with findings from two caregiver surveys, one of which included carers of individuals with other epilepsies (Figure 5).[2,6] Specific aspects of the identified themes could have direct or indirect effects on QoL (e.g., developmental delay has a direct impact and affects the ability to make friends), and certain aspects may have a positive or negative impact, such as treatments (depending on efficacy).[9,68]

In one study, individuals and caregivers (for Dravet syndrome, LGS, or other epilepsies) provided expected patient QoL scores based on a series of hypothetical vignettes. A strong positive correlation was reported between hypothesized patient QoL scores and the number of seizure-free days per month ($p < .001$). Another study assessed patient QoL using a mean health utility score, obtained by converting visual analog scale scores to a 0–1 scale by dividing by 100. This study showed that seizure frequency greatly affected patient QoL, with the lowest reported mean health utility score (.14) being associated with the highest frequency of drop seizures (130 seizures and one seizure-free day per month).[86]

Five studies interviewed parents and caregivers to assess the burden they personally experienced, with multiple countries represented, including Australia, France, Italy, the UK, and the USA.[9,10,86–88] Effects on caregivers were noted in four domains: physical, social, emotional, and work/finances (Figure 5).[9,87]

The reported emotional burden on caregivers was multifaceted; caregivers often went through stages of adjustment after learning that their child had LGS, beginning with disbelief, bargaining, fear, and anger, and followed by acceptance and identity readjustment.[10] Although this burden affects all family members, the greatest burden is experienced by the main caregiver, who is usually the mother of the affected child.[87] Caregivers experience uncertainty around the diagnosis and cause of LGS, seizure activity, treatment efficacy, and prognosis, but parent support groups can reduce isolation and worry, and provide parents with practical advice.[88]

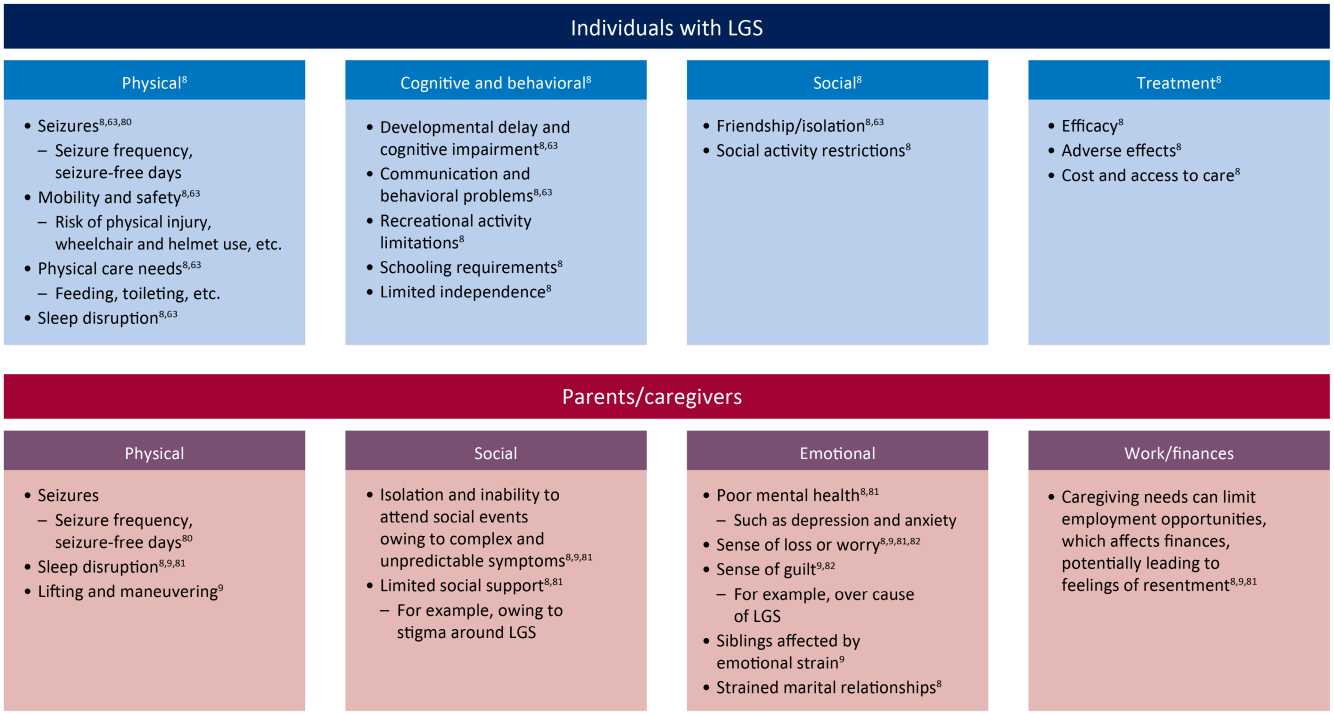

FIGURE 5 Burden experienced by individuals with Lennox–Gastaut syndrome (LGS) and their parents or caregivers.

3.6 | Economic burden

Overall, 13 articles reported on economic burden, with nine studies from the USA and one study each from Germany, Japan, Mexico, and the UK. Of these 13 articles, 11 included information on costs and seven included information on health care usage, with five articles providing information on both (Figure S1). The articles on costs generally focused on direct costs, with little or no information on indirect costs such as lost caregiver productivity and days lost from work.

Direct costs varied considerably across studies, even for studies in the same country. Generally, USA-based studies reported higher per-patient-year costs ($29 911–$80 545) than studies in other countries, including Germany ($24 450.91) and Mexico ($707.34–$2123.25). These costs were often categorized as medical service or pharmacy costs. Medical service costs were generally higher than pharmacy costs; however, there was considerable variation. The main contributor to medical service costs was inpatient costs, which composed 21%–60% of the mean annual health care cost.[67,72,89]

One USA-based study reported a mean (SD) cost of $8147 ($43 218) per medically treated seizure event for Medicaid-insured individuals and $14 759 ($43 600) for commercially insured individuals.[67] Another USA-based study showed that costs for LGS were approximately three times higher than for other epilepsies.[69,90] Pharmacy costs ($1592–$24 018) were mainly driven by the high costs of ASMs, with some evidence of rising costs over time.[69,90–92]

Across five studies, inpatient admissions ranged from .6 to 3.6 per patient-year,[67,69,72,89,93] with a mean length of each hospital stay of 2–5 days.[72,93] Four studies showed that outpatient visits ranged from 6.3 to 11.8 per patient-year.[69,84,89,94]

3.7 | Treatment burden

Most individuals with LGS receive ASMs to manage their symptoms.[23,26,28,30,34,36,42,53,55,60,69,78,80,82,83,88,91,95–100] Across 23 studies with information on LGS treatment, 19 reported that all individuals with LGS received ASMs, and the other four studies generally found that more than 80% of individuals used ASMs. However, pharmacoresistance associated with switching of ASMs[21,23,34,36,39,41,45,49,50,72,73,77,85,92,93,95,96,101–104] and polytherapy[51,105] was common. These findings were consistent for children and adults across several countries, suggesting no difference by demographic or individual characteristics.

Across four studies, 73%–100% of individuals met study-defined criteria for pharmacoresistance.[101,105–107] These four studies covered relatively small samples of children from Italy, Nepal, South Korea, or the USA, but did suggest pharmacoresistance in LGS is not limited

to a particular pediatric age group or geographical location. Polytherapy is usually required,[26,30,60,97,105] with concurrent use of 2–4 ASMs per individual with LGS reported across approximately 40 studies.[18,28,34,36–39,42,44,48–51,53–55,58,66,68,72,73,78,80,81,83,88,90,95,96,98–100,102,104,108–111] Exceptions to the finding that 2–4 ASMs are used concurrently by individuals with LGS were reported in some studies. For example, a UK-based study in 256 individuals with LGS (110 confirmed, 146 probable) estimated a lower mean number of ASMs used per year (approximately one).[93] However, switching of ASMs was common, and the mean total number of ASMs used by individuals with confirmed or probable LGS was 6.7 (SD = 3.4), and 8.5 (SD = 3.5) over a mean follow-up time (averaged across confirmed and probable LGS) of 11.7 (SD = 8.2) years.[93] Six studies reported that individuals with LGS generally used more than four ASMs concurrently,[65,69,84,85,112,113] including one retrospective analysis from the USA ($n = 14\,712$), which used data from the Medicaid multistate database and reported a mean of 5.8 (SD = 2.3) concurrent ASMs after a mean observation period of 11.1 (SD = 4.5) years.[69] These data suggest that use of ASMs can vary widely across individuals with LGS.[65,69,84,85,112,113]

The ASM used by the highest proportion of individuals was valproate or valproic acid (30.8%–100%), with upper estimates for the frequency-of-use range being ≤80% for all other ASMs (Table S7).[23,28,30,34,45,48,49,53,56,58,66,73,77,78,82,85,93,95,98–100,108–110,114] Reported treatment combinations varied, but common combinations across four studies with data were valproate or valproic acid with lamotrigine, clobazam, or levetiracetam.[66,72,74,99] Medications reported by fewer than four studies included drugs approved by the US Food and Drug Administration (FDA) and the European Medicines Agency for use in treatment of epilepsy decades ago (acetazolamide, ethosuximide, mesuximide, oxcarbazepine, phenytoin, and primidone), those with more recent FDA approval (lacosamide and midazolam), and those used off-label to treat epilepsy (cannabis-based medicinal products, intravenous gamma globulin, potassium bromide, and sultiame).[26,34,36,45,48,77,78,93,108,110] Drug–drug interactions were not discussed in the included articles.

ASM discontinuation rates varied across the included studies from less than 5% up to 50%. There were too few studies of each treatment to evaluate whether particular treatments had higher discontinuation rates than others.[39,45,53,73,85,95–98,108,114] Reasons given for discontinuation were aggravated seizure severity or frequency,[95,97,108,114] motor problems,[53] vomiting,[96] and death,[98,108] as well as reasons not related to safety, including lack or loss of efficacy[58,85,98,108] and inability to access the drug.[98] No comparisons were made across treatments on rates or reasons for discontinuation given the limited data for each treatment.

Non-ASM treatments for LGS included ketogenic diet, corpus callosotomy, VNS, focal resection, deep brain stimulation, antipsychotics, and selective serotonin reuptake inhibitors.[18,36,38,39,50,58,77,82,85,91,95,104,105,108–110] Additional treatment modalities are commonly used concurrently with ASMs, with one study from South Korea ($n = 68$) reporting that 61.8% of individuals were receiving non-ASM treatments concurrently with ASMs.[82]

Adverse events (AEs) were associated with treatment with ASMs, corpus callosotomy, dietary changes, and VNS. Commonly reported AEs for ASM treatment were increased seizure frequency, behavioral problems, somnolence, nausea or vomiting, anorexia or decreased appetite, weight loss, rash, and dizziness.[45,53,58,95,98,108–110,114–116]

For VNS, AEs tended to occur soon after surgical implantation of the device and to resolve over time.[85,104] Common AEs with VNS included problems related to the respiratory system and speaking, including voice alteration or hoarseness, drooling, and coughing.[28,37,73,85,111] For corpus callosotomy, two studies reported AEs, which related to brain connections (e.g., acute disconnection syndrome, aphasia, ataxia, and paresis).[28,111] AEs related to dietary therapy were reported in two studies, and were mainly gastrointestinal, including vomiting, diarrhea, constipation, and weight loss, as well as metabolic acidosis.[56,96]

4 | DISCUSSION

Evaluating the literature on the burden of illness of LGS is critical to identifying evidence gaps and guiding further research, which can positively affect individuals, caregivers, health care systems, and society. Overall, the literature reviewed here suggests that the high symptom burden of LGS has wide-ranging negative effects on patients and their caregivers. For example, the high seizure frequency not only decreases patient QoL, but is also associated with a high economic cost and a requirement for assistance with a range of everyday activities that place a substantial burden on caregivers. Severe or profound developmental delay, motor deficits, and problems with communication were present in a large number of patients with LGS. Pharmacoresistance, polytherapy, and treatment-switching are common, with individuals typically taking more than two ASMs at any one time. Although the potential impact of COVID-19 on LGS was captured in the search terms, no studies reported on this domain, and it is therefore not further discussed in this review.

Individuals with LGS experience a high clinical symptom burden from both seizure and nonseizure symptoms. However, more articles focused on clinical symptom

burden of seizures and treatment burden (72 and 67 articles, respectively) than on nonseizure symptoms and comorbidities (46 and 12 articles, respectively). Seizure onset in infancy, high seizure frequency, and presentation with multiple seizure types all contribute to substantial care requirements, negative impacts on patient QoL, and a significant humanistic burden for caregivers. Nonseizure symptoms, including developmental delay, difficulties with communication and sleep, impaired motor ability, intellectual disability, and psychiatric and behavioral problems, as well as multiple comorbidities such as autism, blindness, and cerebral palsy, all contribute to a high humanistic burden and lower patient QoL.

Disentangling nonseizure symptoms from comorbidities is often difficult, as evidenced by the overlap of terminology observed in the included articles. When reported as nonseizure symptoms, many individuals with LGS had developmental delay, with eight studies reporting a prevalence of 79.6%–100%. Intellectual disability was also common, with 19 studies reporting a prevalence of at least 90%. In comparison, when described as comorbidities, the range of prevalence estimates reported for developmental delay by two studies was wider (50%–100%), whereas a lower range of prevalence estimates was reported for intellectual disorders, again by two studies (53%–67%). As a result, the true range of prevalence estimates for nonseizure symptoms/comorbidities experienced by individuals with LGS may not be fully captured without considering this overlap in terminology. Additionally, multiple types of motor deficits with varying prevalence were reported, reflecting the complex presentation of LGS. Although a high prevalence of problems with communication and sleep was observed in individuals with LGS, few studies assessed these symptoms in detail.

In general, both nonseizure symptoms and comorbidities were underrepresented in the literature, and accurate assessment was further confounded by overlap in terminologies and the classification of some causes of LGS, such as tuberous sclerosis, as comorbidities. The paucity of information on nonseizure symptoms and comorbidities of LGS make them promising areas for further research, which could inform development of new treatments or help determine when existing treatments may be effective, ultimately improving the QoL of both patients and caregivers.

Individuals with LGS experience a high treatment burden owing to pharmacoresistance,[101,105–107] polytherapy,[26,30,60,97,105] and frequent treatment-switching.[21,23,34,36,39,41,45,49,50,72,73,77,85,92,93,95,96,101–104] Available treatments are associated with multiple AEs, although these tend to be mild, with few severe or serious AEs reported.[45,53,58,95,98,108–110,114–116] Common combinations of ASMs identified included valproate or valproic acid with lamotrigine, clobazam, or levetiracetam.[1,66,74,99] Use of cannabis-based medicinal products was reported in one study[77]; no studies included here reported on cannabidiol use. However, drugs such as cannabidiol, which received FDA approval in 2020, have not been in clinical practice long enough for observational studies to have been published. Nonetheless, most available treatments target the seizure symptoms of LGS and a need remains for treatments that also target nonseizure symptoms, which could potentially alleviate some of the humanistic burden experienced by individuals.

Few studies reported on caregiver burden ($n = 5$) or humanistic burden ($n = 3$). The present review identified several studies that reported impact of LGS on patients, with limited independence, restriction in social activities, and lack of friendship/isolation all shown to negatively affect QoL.[9,68] In addition, a similar trend was found for caregivers, with limited employment opportunities, poor mental health, and strained marital relationships being among the negative effects experienced.[9,10,87] Although three articles in this review reported on QoL for individuals with LGS,[9,68,86] these studies used questionnaires completed by caregivers rather than validated tools and, given the hypothetical nature of the scenarios, the results may be subject to bias. Development of a reliable disease-specific tool for measuring QoL could enable more effective evaluation of interventions than is possible with existing generic measures.

Although based on limited data, the identified caregiver requirements and burden were substantial, with individuals with LGS requiring assistance with everyday mobility and self-care functions. Moreover, because many individuals with LGS are unable to live independently or to support themselves economically, many caregivers are required to provide lifelong assistance that negatively affects their own employment opportunities and finances, which can lead to feelings of resentment.[9,10] No studies included in this review comprehensively assessed how caring for a patient with LGS can affect workplace productivity, making this an area for potential further research.

Much of the economic burden of LGS derives from the high cost of medications and frequent hospital stays, which contribute to the direct costs for LGS being threefold higher than those for other epilepsies.[69,90] Variation in the direct costs of LGS was observed even when restricting to studies from the same country, and there was no clear trend in change with time, suggesting that more work is needed to determine the true cost of LGS. However, the results presented should be interpreted in the context of potential data-quality concerns regarding sample representativeness, LGS definitions, and the clarity of the reporting. Additionally, the overrepresentation

of USA-based sources may decrease the generalizability of the economic burden findings of LGS across countries, because of variation in health care models (e.g., absence of treatment reimbursement systems in some countries). However, it is clear that the economic burden and health care resource use associated with LGS may negatively affect individuals, caregivers, and society.

Comparing findings across studies was often challenging owing to unclear selection criteria, limited details on the case definition for LGS, and lack of confirmation for LGS diagnoses. Moreover, variations in diagnostic criteria for LGS across studies reflect changes to the definition of LGS and associated diagnostic criteria over time, further confounding efforts to compare studies. Consequently, it was difficult to determine whether any identified heterogeneity across studies reflected true heterogeneity in the population or artifactual differences in study methodologies. The LGS electroclinical phenotype shows a high degree of heterogeneity, and LGS diagnoses may encompass multiple separate conditions with different etiologies, genotypes, risks of mortality/sudden unexpected death in epilepsy, and treatment requirements. Additionally, all included studies were published before the introduction in 2022 of updated seizure definitions,[3] so the accuracy of distinguishing different seizure types may have been suboptimal.[27,29] This heterogeneity may explain the variation in the findings of this review but hinders a definitive assessment of the true burden of illness of LGS. The introduction of updated diagnostic criteria[3] may help to improve the diagnostic framework going forward; however, without a biomarker or genetic cause, the diagnosis of LGS remains differential and, therefore, prone to subjectivity.[4]

The key strength of this review is the comprehensive analysis of the burden of LGS in several areas, from the perspective of individuals and caregivers. Data were retrieved for all planned domains of burden in LGS, with the exception of the impact of the COVID-19 pandemic on patients and caregivers. The present review also identified areas in which the burden of LGS could be reduced, including development of treatments targeting nonseizure symptoms. Limitations include issues with sample representativeness, disease and outcomes measures, and the clarity of the reporting in some articles. Another limitation of this review is the exclusion of randomized controlled trials from the searches, which were excluded to ensure that the review would provide an overview of the burden of LGS in a real-world setting. Randomized controlled trials could provide more representative samples of patients based on clear diagnostic criteria, as well as a greater insight into the AEs experienced by individuals with LGS, because AEs are usually more thoroughly assessed in these studies.

Future studies should aim to include representative samples of the LGS population and to use clearly defined selection criteria that are generalizable across all individuals with LGS. In addition, use of updated diagnostic criteria would allow accurate identification of individuals with LGS.

5 | CONCLUSIONS

LGS is associated with a high burden across several interlinked domains, with factors such as the clinical symptom burden and incidence of nonseizure symptoms and comorbidities resulting in both low QoL for individuals with LGS and considerable burden on caregivers. Key areas for further research are development of treatments that address nonseizure symptoms and overcome the pharmacoresistance commonly observed in LGS, development of a disease-specific tool for measuring QoL of individuals with LGS, and comprehensive assessment of the effect of LGS on caregiver work productivity. Additionally, standardization of LGS definitions and recognition, clear assessment of nonseizure symptoms, and harmonization of high-quality study methods across studies are needed to address the quality concerns identified in this review.

AUTHOR CONTRIBUTIONS

All authors contributed to the study conception and design, interpreted the results, contributed to the writing of the manuscript, and approved the final version of the manuscript for submission.

ACKNOWLEDGMENTS

This review was funded by the sponsor, Takeda Pharmaceutical Company. Under the direction of the authors and funded by Takeda Pharmaceutical Company, William Luderman, PhD, Erin Aldera, PhD, and Adam Hargreaves, PhD of Oxford PharmaGenesis, Oxford, UK, provided writing assistance for this publication, in accordance with current Good Publication Practice guidelines. Editorial assistance in formatting, proofreading, copyediting, and fact-checking was also provided by Oxford PharmaGenesis.

CONFLICT OF INTEREST STATEMENT

A.B., J.S.A., and D.S. are employees of Takeda Pharmaceutical Company and own stock or stock options. J.R. is an employee of Novo Nordisk Healthcare and a former employee of Takeda Pharmaceutical Company. A.J. is an employee of Oxford PharmaGenesis, Oxford, UK. E.B. is a former employee of Oxford PharmaGenesis, Oxford, UK. The following authors have received compensation for serving as consultants or speakers, or they

or the institutions they work for have received research support or royalties from the companies or organizations indicated: J.H.C. (Biocodex, Engineering and Physical Sciences Research Council [UK], Epilepsy Research UK, Great Ormond Street Hospital Children's Charity, GW Pharmaceuticals/Jazz Pharmaceuticals, Marinus Pharmaceuticals, National Institute for Health and Care Research, National Institute of Health Research Biomedical Research Centre at Great Ormond Street Hospital, Nutricia, Ovid Therapeutics, Stoke Therapeutics, UCL Great Ormond Street Institute of Child Health, Ultragenyx, Vitaflo, Waterloo Foundation, and Zogenix/UCB) and J.S. (BioPharm Solutions, Bright Minds, CAMP4 Therapeutics, Dravet Syndrome Foundation, Encoded Therapeutics, Epilepsy Study Consortium, Epygenix Therapeutics, Greenwich Biosciences, Longboard Pharmaceuticals, Marinus Pharmaceuticals, Neurocrine Biosciences, PCDH19 Alliance, Praxis, Stoke Therapeutics, Takeda, Xenon Pharmaceuticals, and Zogenix). We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

DATA AVAILABILITY STATEMENT

All relevant data from the original articles are included in this review, and citations are provided to indicate the original source for all information.

ORCID

J. Helen Cross https://orcid.org/0000-0001-7345-4829
Aimee Jones https://orcid.org/0000-0003-0279-1814
Joseph Sullivan https://orcid.org/0000-0003-2081-8988

REFERENCES

1. Strzelczyk A, Schubert-Bast S. Expanding the treatment landscape for Lennox-Gastaut syndrome: current and future strategies. CNS Drugs. 2021;35:61–83.
2. Asadi-Pooya AA. Lennox-Gastaut syndrome: a comprehensive review. Neurol Sci. 2018;39:403–14.
3. Specchio N, Wirrell EC, Scheffer IE, Nabbout R, Riney K, Samia P, et al. International league against epilepsy classification and definition of epilepsy syndromes with onset in childhood: position paper by the ILAE task force on nosology and definitions. Epilepsia. 2022;63:1398–442.
4. Bourgeois BF, Douglass LM, Sankar R. Lennox-Gastaut syndrome: a consensus approach to differential diagnosis. Epilepsia. 2014;55(Suppl 4):4–9.
5. Resnick T, Sheth RD. Early diagnosis and treatment of Lennox-Gastaut syndrome. J Child Neurol. 2017;32:947–55.
6. Cross JH, Auvin S, Falip M, Striano P, Arzimanoglou A. Expert opinion on the Management of Lennox–Gastaut Syndrome: treatment algorithms and practical considerations. Front Neurol. 2017;8:505.
7. Chipaux M, Szurhaj W, Vercueil L, Milh M, Villeneuve N, Cances C, et al. Epilepsy diagnostic and treatment needs identified with a collaborative database involving tertiary centers in France. Epilepsia. 2016 May;57:757–69.
8. Gallop K, Wild D, Nixon A, Verdian L, Cramer JA. Impact of Lennox-Gastaut syndrome (LGS) on health-related quality of life (HRQL) of patients and caregivers: literature review. Seizure. 2009;18:554–8.
9. Gallop K, Wild D, Verdian L, Kerr M, Jacoby A, Baker G, et al. Lennox-Gastaut syndrome (LGS): development of conceptual models of health-related quality of life (HRQL) for caregivers and children. Seizure. 2010;19:23–30.
10. Gibson PA. Lennox-Gastaut syndrome: impact on the caregivers and families of patients. J Multidiscip Healthc. 2014;7:441–8.
11. Strzelczyk A, Zuberi SM, Striano P, Rosenow F, Schubert-Bast S. The burden of illness in Lennox–Gastaut syndrome: a systematic literature review. Orphanet J Rare Dis. 2023;18:42.
12. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021;29(372):n71.
13. von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP, et al. The strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies. Ann Intern Med. 2007;16(147):573–7.
14. Downes MJ, Brennan ML, Williams HC, Dean RS. Development of a critical appraisal tool to assess the quality of cross-sectional studies (AXIS). BMJ Open. 2016;8(6):e011458.
15. Luchini C, Stubbs B, Solmi M, Veronese N. Assessing the quality of studies in meta-analyses: advantages and limitations of the Newcastle Ottawa scale. World J Meta-Anal. 2017;5:80–123.
16. Fisher RS, Cross JH, French JA, Higurashi N, Hirsch E, Jansen FE, et al. Operational classification of seizure types by the international league against epilepsy: position paper of the ILAE Commission for Classification and Terminology. Epilepsia. 2017;58:522–30.
17. Deering L, Medicine WC, Hesdorffer DC, Columbia University Medical Center, Nelson A, Center NYULM, et al. Mind the gap: the evolution of Lennox–Gastaut syndrome. Baltimore, USA: American Epilepsy Society Annual Meeting 2019; 2019.
18. Sondhi V, Chakrabarty B, Jauhari P, Gupta A, Gulati S. Clinical profile and outcome of children with lennox gastaut syndrome: Retrospective single centre cohort Neurology 90. 2018.
19. Nikanorova M, Miranda M. Electroclinical Semiology at Onset of the Lennox-Gastaut Syndrome. Epilepsia. 2009;50:149.
20. Furune S, Watanabe K, Negoro T, Miyazaki S, Takeuchi T, Matsumoto A, et al. Long-term prognosis and clinico-electroencephalographic evolution of Lennox-Gastaut syndrome. Brain Dysfunction. 1988;1:146–53.
21. Hoffmann-Riem M, Diener W, Benninger C, Rating D, Unnebrink K, Stephani U, et al. Nonconvulsive status epilepticus—a possible cause of mental retardation in patients with Lennox-Gastaut syndrome. Neuropediatrics. 2000;31:169–74.
22. Widdess-Walsh P, Joshi S, Geller EB, EPGP Senior Investigators. Cryptogenic lennox-gastaut syndrome: phenotypic characteristics of participants in the epilepsy phenome/genome project (Abs 1.150). Epilepsy Curr. 2012;12(Suppl 1):60.
23. Lemmon ME, Terao NN, Ng YT, Reisig W, Rubenstein JE, Kossoff EH. Efficacy of the ketogenic diet in Lennox-Gastaut syndrome: a retrospective review of one institution's

experience and summary of the literature. Dev Med Child Neurol. 2012;54:464–8.
24. Pati S, Deep A, Troester MM, Kossoff EH, Ng YT. Lennox-Gastaut syndrome symptomatic to hypothalamic hamartoma: evolution and long-term outcome following surgery. Pediatr Neurol. 2013;49:25–30.
25. Trevathan E, Murphy CC, Yeargin-Allsopp M. Prevalence and descriptive epidemiology of Lennox-Gastaut syndrome among Atlanta children. Epilepsia. 1997;38:1283–8.
26. Ekici A, Yarar C, Yakut A, Carman KB, Yimenicioglu S. Lennox-Gastaut sendromlu hastaların klinik özellikleri ve uzun süreli seyri. Turk Pediatri Arsivi. 2012;47:47–51.
27. Yagi K. Evolution of Lennox-Gastaut syndrome: a long-term longitudinal study. Epilepsia. 1996;37:48–51.
28. Katagiri M, Iida K, Kagawa K, Hashizume A, Ishikawa N, Hanaya R, et al. Combined surgical intervention with vagus nerve stimulation following corpus callosotomy in patients with Lennox-Gastaut syndrome. Acta Neurochir. 2016;158:1005–12.
29. Fitzgerald LF, Stone JL, Hughes JR, Melyn MA, Lansky LL. The Lennox-Gastaut syndrome: electroencephalographic characteristics, clinical correlates, and follow-up studies. Clin EEG Electroencephal. 1992;23:180–8.
30. Herranz JL, Casas-Fernandez C, Campistol J, Campos-Castello J, Rufo-Campos M, Torres-Falcon A, et al. Lennox-Gastaut syndrome in Spain: a descriptive retrospective epidemiological study. Rev Neurol. 2010;50:711–7.
31. Horita H, Kumagai K, Maekawa K. Overnight polygraphic study of Lennox-Gastaut syndrome. Brain and Development. 1987;9:627–35.
32. Asadi-Pooya AA, Sharifzade M. Lennox–Gastaut syndrome in south Iran: electroclinical manifestations. Seizure. 2012;21:760–3.
33. Ouedraogo PV, Boudzoumou DBE, Ngoma KHC, Ndiaye M. Electro-Clinical Manifestations of Lennox-Gastaut syndrome. Afr J Neurol Sci. 2018;37:24–31.
34. Rodriguez-Rodriguez S, Salas-Puig J, Alvarez-Carriles JC, Temprano-Fernandez T, Gonzalez CA, Garcia-Martinez A. Development of Lennox-Gastaut syndrome in adulthood. Rev Neurol. 2011;52:257–63.
35. Ren LK, Wu LW, Jin LR, Gao W, Shao XQ. Characteristics of clinical manifestations and EEG of Lennox-Gastaut syndrome. J Pediatr. 2003;41:7–10.
36. Vignoli A, Oggioni G, De Maria G, Peron A, Savini MN, Zambrelli E, et al. Lennox-Gastaut syndrome in adulthood: long-term clinical follow-up of 38 patients and analysis of their recorded seizures. Epilepsy Behav. 2017;77:73–8.
37. Suller Marti A, Mirsattari SM, MacDougall K, Steven DA, Parrent A, de Ribaupierre S, et al. Vagus nerve stimulation in patients with therapy-resistant generalized epilepsy. Epilepsy Behav. 2020;111:107253.
38. Asadi-Pooya AA, Bazrafshan M, Farazdaghi M. Long-term medical and social outcomes of patients with Lennox-Gastaut syndrome. Epilepsy Res. 2021;178:106813.
39. Kessler SK, McCarthy A, Cnaan A, Dlugos DJ. Retention rates of rufinamide in pediatric epilepsy patients with and without Lennox–Gastaut syndrome. Epilepsy Res. 2015;112:18–26.
40. Liu SY, An N, Fang X, Singh P, Oommen J, Yin Q. Surgical treatment of patients with Lennox-Gastaut syndrome phenotype. Sci World J. 2012;2012:614263.
41. Rodriguez Mendoza M, Martinez Montiel X, Luevano JJ, Vanegas MA. Effectiveness of the corpus callosotomy as a quirurgical treatment for the Lennox-Gastaut syndrome. Epileptic Disord. 2014;16:22.
42. Ferlazzo E, Nikanorova M, Italiano D, Bureau M, Dravet C, Calarese T, et al. Lennox-Gastaut syndrome in adulthood: clinical and EEG features. Epilepsy Res. 2010;89:271–7.
43. Ogawa K, Kanemoto K, Ishii Y, Koyama M, Shirasaka Y, Kawasaki J, et al. Long-term follow-up study of Lennox–Gastaut syndrome in patients with severe motor and intellectual disabilities: with special reference to the problem of dysphagia. Seizure. 2001;10:197–202.
44. Spoor JKH, Greco T, Kamp MA, Faini S, Senft C, Dibue M. Quantifying the burden of disease in patients with Lennox Gastaut syndrome. Epilepsy Behav Rep. 2021;16:100508.
45. Nikanorova M, Brandt C, Auvin S, McMurray R. Real-world data on rufinamide treatment in patients with Lennox-Gastaut syndrome: results from a European noninterventional registry study. Epilepsy Behav. 2017;76:63–70.
46. Papini M, Pasquinelli A, Armellini M, Orlandi D. Alertness and incidence of seizures in patients with Lennox-Gastaut syndrome. Epilepsia. 1984;25:161–7.
47. De Santis R, Sadoway T, Andrade D. Genetic characterization and prognosis of adult patients with Lennox-Gastaut syndrome: a prospective case-series study (P2.5-011). 2019.
48. Zamponi N, Passamonti C, Cesaroni E, Trignani R, Rychlicki F. Effectiveness of vagal nerve stimulation (VNS) in patients with drop-attacks and different epileptic syndromes. Seizure. 2011;20:468–74.
49. Nikanorova M, Panzer A, Chouette I. A European Registry of antiepileptic drug use in patients with Lennox-Gastaut syndrome: update of current status. Epilepsia. 2011;52:132.
50. Lee S, Baek MS, Lee YM. Lennox-Gastaut syndrome in mitochondrial disease. Yonsei Med J. 2019;60:106–14.
51. Soto A, Contreras G, Sainz V, Rubio E, Scholtz H, Hernandez O, et al. Vagus nerve stimulation (VNS) therapy in 46 patients with lennox-gastaut syndrome (LGS) in Venezuela. Epilepsy Curr. 2014;14:407.
52. Fitzgerald MP, Kaufman MC, Massey SL, Fridinger S, Prelack M, Ellis C, et al. Assessing seizure burden in pediatric epilepsy using an electronic medical record-based tool through a common data element approach. Epilepsia. 2021;62:1617–28.
53. Grosso S, Coppola G, Cusmai R, Parisi P, Spalice A, Foligno S, et al. Efficacy and tolerability of add-on lacosamide in children with Lennox-Gastaut syndrome. Acta Neurol Scand. 2014;129:420–4.
54. Jamil A, Levinson N, Gelfand M, Hill CE, Khankhanian P, Davis KA. Efficacy and tolerability of Clobazam in adults with drug-refractory epilepsy. Neurol Clin Pract. 2021;11:e669–e676.
55. Kumar A, Paliwal VK, Agarwal V, Neyaz Z, Lal H, Goel G. Relationship of Lennox-Gastaut syndrome with perinatal event: a cross-sectional study. J Pediatr Neurosci. 2015;10:98–102.
56. Na JH, Kim HD, Lee YM. Effective and safe diet therapies for Lennox-Gastaut syndrome with mitochondrial dysfunction. Ther Adv Neurol Disord. 2020;13:175628641989781.
57. Oka E, Sanada S, Asano T, Ishida T. Mental deterioration in childhood epilepsy. Acta Med Okayama. 1997;51:173–8.
58. Reyhani A, Ozkara C. The unchanging face of Lennox-Gastaut syndrome in adulthood. Epilepsy Res. 2021;172:106575.

59. Brinciotti M, Matricardi M, Curatolo P. Prognosis of Lennox-Gastaut syndrome. Minerva Pediatr. 1981;33:105–10.
60. He N, Li BM, Li ZX, Wang J, Liu XR, Meng H, et al. Few individuals with Lennox-Gastaut syndrome have autism spectrum disorder: a comparison with Dravet syndrome. J Neurodev Disord. 2018;10:10.
61. Uysal U, Liu M, Fountain NB. Prospective analysis of seizure freedom in established epilepsy (Abs 1.160). Epilepsy Curr. 2012;12(Suppl 1):64.
62. Goldsmith IL, Zupanc ML, Buchhalter JR. Long-term seizure outcome in 74 patients with Lennox-Gastaut syndrome: effects of incorporating MRI head imaging in defining the cryptogenic subgroup. Epilepsia. 2000;41:395–9.
63. Milovanovic M, Martinovic Z. Lennox-gastaut syndrome in adult patients. Epilepsia. 2014;55:207–8.
64. Oguni H, Hayashi K, Osawa M. Long-term prognosis of Lennox-Gastaut syndrome. Epilepsia. 1996;37:44–7.
65. Eschbach K, Moss A, Joshi C, Angione K, Smith G, Dempsey A, et al. Diagnosis switching and outcomes in a cohort of patients with potential epilepsy with myoclonic-atonic seizures. Seizures Epilepsy Res. 2018;147:95–101.
66. Rathaur BPS, Garg RK, Verma R, Malhotra HS, Sharma PK, Kumar R. Clinical demographic profile and outcome of patients with Lennox-Gastaut syndrome (LGS). Ann Indian Acad Neurol. 2014;17:S203–S204.
67. Reaven NL, Funk SE, Lyons PD, Story TJ. The direct cost of seizure events in severe childhood-onset epilepsies: a retrospective claims-based analysis. Epilepsy Behav. 2019;93:65–72.
68. Dixon-Salazar T, Huntley M, SanInocencio C. Lennox-Gastaut syndrome: characteristics and major caregiver concerns (LGS). New Orleans, LA: American Epilepsy Society; 2018.
69. Pina-Garza JE, Montouris GD, Vekeman F, Cheng WY, Tuttle E, Giguere-Duval P, et al. Assessment of treatment patterns and healthcare costs associated with probable Lennox-Gastaut syndrome. Epilepsy Behav. 2017;73:46–50.
70. Berg AT, Gaebler-Spira D, Wilkening G, Zelko F, Knupp K, Dixon-Salazar T, et al. Nonseizure consequences of Dravet syndrome, KCNQ2-DEE, KCNB1-DEE, Lennox-Gastaut syndrome, ESES: a functional framework. Epilepsy Behav. 2020;111:107287.
71. Kieffer-Renaux V, Jambaque I, Kaminska A, Dulac O. Neuropsychological outcome of children with Lennox-Gastaut and doose syndromes. ANAE. 1997;9:84–8.
72. Strzelczyk A, Schubert-Bast S, Simon A, Wyatt G, Holland R, Rosenow F. Epidemiology, healthcare resource use, and mortality in patients with probable Lennox-Gastaut syndrome: a population-based study on German health insurance data. Epilepsy Behav. 2021;115:107647.
73. Kostov K, Kostov H, Tauboll E. Long-term vagus nerve stimulation in the treatment of Lennox–Gastaut syndrome. Epilepsy Behav. 2009;16:321–4.
74. Habib HS. Clinical characteristics and responsiveness to treatment in Lennox-Gastaut syndrome. A retrospective hospital audit. Neurosciences. 2006;11:24–7.
75. Hsairi I, Ayadi I, Jardak F, Abid I, Kammoun F, Triki C. Childhood epileptic encephalopathies: cognitive and behavioural aspects. J Neurol. 2011;258:S234.
76. Boel MJC. Behavioural and neuropsychological problems in refractory paediatric epilepsies. Eur J Peadiratr Neurol. 2004;8:291–7.
77. Smith KM, Britton JW, Cascino GD. Late-onset Lennox-Gastaut syndrome: diagnostic evaluation and outcome. Neurol Clin Pract. 2018;8:397–402.
78. Amir N, Shalev RS, Steinberg A. Sleep patterns in the Lennox-Gastaut syndrome. Neurology. 1986;36:1224–6.
79. Eisensehr I, Parrino L, Noachtar S, Smerieri A, Terzano MG. Sleep in Lennox-Gastaut syndrome: the role of the cyclic alternating pattern (CAP) in the gate control of clinical seizures and generalized polyspikes. Epilepsy Res. 2001;46:241–50.
80. Velasco M, Diaz-de-Leon AE, Brito F, Velasco AL, Velasco F. Sleep-epilepsy interactions in patients with intractable generalized tonic seizures and depth electrodes in the centro median thalamic nucleus. Arch Med Res. 1995;26:S117–S125.
81. Segovia BL. Malnutrition, an important comorbidity in patients with Lennox Gastaut syndrome. J Neurol Neurosurg. 2017;3:3.
82. Kim HJ, Kim HD, Lee JS, Heo K, Kim DS, Kang HC. Long-term prognosis of patients with Lennox—Gastaut syndrome in recent decades. Epilepsy Res. 2015;110:10–9.
83. Berg AT, Kaat AJ, Zelko F, Wilkening G. Rare diseases – rare outcomes: assessing communication abilities for the developmental and epileptic encephalopathies. Epilepsy Behav. 2022;128:108586.
84. Pina-Garza JE, Vekeman F, Cheng W, Tuttle E, Giguere-Duval P, Oganisian A, et al. Development of a claims-based classifier to identify Lennox-Gastaut syndrome. Neurology. 2015;84(P7):30.
85. Frost M, Gates J, Helmers SL, Wheless JW, Levisohn P, Tardo C, et al. Vagus nerve stimulation in children with refractory seizures associated with Lennox-Gastaut syndrome. Epilepsia. 2001;42:1148–52.
86. Auvin S, Damera V, Martin M, Holland R, Simontacchi K, Saich A. The impact of seizure frequency on quality of life in patients with Lennox-Gastaut syndrome or Dravet syndrome. Epilepsy Behav. 2021;123:108239.
87. Cramer J, Gallop K, Wild D, Falconer S, Verdian L. Domains of concern for families whose child has Lennox-Gastaut syndrome. Epilepsia. 2009;50:177.
88. Murray J. Coping with the uncertainty of uncontrolled epilepsy. Seizure. 1993;2:167–78.
89. Swindle JP, Song R, Liu F, Adams S. PND13 economic burden of Lennox-Gastaut syndrome. Value Health. 2012;15:A143.
90. Stockl KM, Hollenack KA, Acs A, Tran O, Krol J, Story TJ. PND27 economic burden of probable lennox-gastaut syndrome, probable dravet syndrome, and other refractory epilepsies for United States commercial health plans. Value Health. 2019;22:S274.
91. Montouris G, Pina-Garza JE, Vekeman F, Cheng WY, Tuttle EG, Giguere-Duval P, et al. A life-course assessment of medication use and medical costs of lennox-gastaut syndrome (LGS). Value Health. 2016;19:A67–A68.
92. Hollenack KA, Story TJ, Acs A, Tran O, Krol J, Stockl KM. PND34 economic burden of probable Lennox-Gastaut syndrome, probable dravet syndrome, and other refractory epilepsies for united states medicaid health plans. Value Health. 2019;22:S276.
93. Chin RFM, Pickrell WO, Guelfucci F, Martin M, Holland R. Prevalence, healthcare resource utilization and mortality of Lennox-Gastaut syndrome: retrospective linkage cohort study. Seizure. 2021;91:159–66.
94. Li X, Knoth R. Examining healthcare utilization and costs in patients with lennox-gastaut syndrome: a real-world

observational study in a U.S. health plan. J Manag Care Spec Pharm. 2015;21:S48.
95. Andrade-Machado R, los Reyes J L-N-d, Benjumea-Cuartas V, Restrepo JFA, Jaramillo-Jimenez E, Andrade-Gutierrez G, et al. Efficacy and tolerability of add-on Lacosamide treatment in adults with Lennox–Gastaut syndrome: an observational study. Seizure. 2015;33:81–7.
96. Nickels K, Kenney D, Eckert S, Wong-Kisiel L, Wirrell E. Ketogenic diet efficacy in children with Lennox–Gastaut syndrome. J Neurol Sci. 2013;333:e13.
97. Auvin S, Papon A, Bellavoine V, Storme T, Merdariu D, Ilea A, et al. Use of adjunctive rufinamide for patients with lennox-gastaut syndrome in clinical practice. Epilepsia. 2014;55:111.
98. Lee EH, Yum M-S, Choi H-W, Ko T-S. Long-term use of Clobazam in Lennox-Gastaut syndrome: experience in a single tertiary epilepsy center. Clin Neuropharmacol. 2013;36:4–7.
99. Rathaur BP, Garg RK, Malhotra HS, Kumar N, Sharma PK, Verma R, et al. Lennox-Gastaut syndrome: a prospective follow-up study. J Neurosci Rural Pract. 2017;8:225–7.
100. Aljaafari D, Fasano A, Nascimento FA, Lang AE, Andrade DM. Adult motor phenotype differentiates Dravet syndrome from Lennox-Gastaut syndrome and links SCN1A to early onset parkinsonian features. Epilepsia. 2017;58:e44–e48.
101. Kim H, Yoo S, Jeon Y, Yi S, Kim S, Choi SA, et al. Characterization of anti-seizure medication treatment pathways in pediatric epilepsy using the electronic health record-based common data model. Front Neurol. 2020;11:409.
102. Asadi-Pooya AA, Malekmohamadi Z, Kamgarpour A, Rakei SM, Taghipour M, Ashjazadeh N, et al. Corpus callosotomy is a valuable therapeutic option for patients with Lennox-Gastaut syndrome and medically refractory seizures. Epilepsy Behav. 2013;29:285–8.
103. Shih EJ, Murata K, Hussain S. The ketogenic diet in the treatment of highly refractive infantile spasms and lennox-gastaut syndrome. J Investig Med. 2015;63:180–1.
104. Abdelmoity SA, Abdelmoity AA, Riordan SM, Kaufman C, Le Pichon JB, Abdelmoity A. The efficacy and tolerability of autostimulation-VNS in children with Lennox-Gastaut syndrome. Seizure. 2021;86:168–74.
105. Oggioni GD, Scornavacca G, Allaria F, Zambrelli E, Chiesa V, Vignoli A, et al. Lennox-Gastaut syndrome in adulthood: clinical features from a long term follow-up. Epilepsia. 2014;55:211.
106. Berg AT, Levy SR, Testa FM. Evolution and course of early life developmental encephalopathic epilepsies: focus on Lennox-Gastaut syndrome. Epilepsia. 2018;59:2096–105.
107. Poudel P, Kafle SP, Pokharel R. Clinical profile and treatment outcome of epilepsy syndromes in children: a hospital-based study in eastern Nepal. Epilepsia Open. 2021;6:206–15.
108. Lee EH, Yum MS, Ko TS. Effectiveness and tolerability of rufinamide in children and young adults with Lennox–Gastaut syndrome: a single center study in Korea. Clin Neurol Neurosurg. 2013;115:926–9.
109. Takayama R, Fukumura S, Minagawa K, Watanabe T. Short-Term Efficacy and Safety of Rufinamide for Lennox-Gastaut Syndrome. Brain and Development. 2016;48:332–6.
110. You SJ, Kang HC, Kim HD, Lee HS, Ko TS. Clinical efficacy of zonisamide in Lennox-Gastaut syndrome: Korean multicentric experience. Brain and Development. 2008;30:287–90.
111. You SJ, Kang HC, Ko TS, Kim HD, Yum MS, Hwang YS, et al. Comparison of corpus callosotomy and vagus nerve stimulation in children with Lennox-Gastaut syndrome. Brain and Development. 2008;30:195–9.
112. Kang JW, Eom S, Hong W, Kwon HE, Park S, Ko A, et al. Long-term outcome of resective epilepsy surgery in patients with Lennox-Gastaut syndrome. Pediatrics. 2018;142:e20180449.
113. LoPresti M, Murofushi T, Claxton L, Marshall J. PND14 identifying patients with RARE refractory epilepsies in Japanese health databases: feasibility for a burden of illness study value in health regional issues 2020; 22:S77.
114. Kim SH, Kang H-C, Lee JS, Kim HD. Rufinamide efficacy and safety in children aged 1–4 years with Lennox–Gastaut syndrome. Brain and Development. 2018;40:897–903.
115. Kim SH, Eun SH, Kang HC, Lee JS, Kim HD. Adjunctive therapy of rufinamide in Lennox-Gastaut syndrome. Epilepsia. 2011;52:209.
116. Kwon S, Hwang SK, Kang BH. Effectiveness and tolerability of rufinamide in Korean children with Lennox-Gastaut syndrome. Epilepsia. 2015;56:169–70.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Cross JH, Benítez A, Roth J, Andrews JS, Shah D, Butcher E, et al. A comprehensive systematic literature review of the burden of illness of Lennox–Gastaut syndrome on patients, caregivers, and society. Epilepsia. 2024;00:1–16. https://doi.org/10.1111/epi.17932