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Understanding the Burden of Lennox–Gastaut Syndrome: Implications for Patients, Caregivers, and Society in High and Low Resource Settings: A Narrative Review

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ABSTRACT

Background: Lennox–Gastaut syndrome (LGS) poses significant challenges in diagnosis, management, and treatment due to its rare nature, diverse presentation, and drug-resistant seizures. While classical features aid diagnosis, challenges persist, impacting patient care and outcomes. Understanding the syndrome's burden is essential for improving healthcare policies and interventions.

Aim: This literature review aimed to comprehensively analyze clinical symptom burden, comorbidities, care requirements, quality of life (QoL), economic burden, caregiver burden, and treatment burden to pinpoint knowledge gaps for future research and intervention development, ultimately aiming to enhance the well-being of patients and caregivers.

Methods: A comprehensive literature review was conducted using electronic databases and manual searches to analyze clinical symptom burden, comorbidities, care requirements, QoL, economic burden, caregiver burden, and treatment burden associated with LGS.

Results: LGS significantly impacts the QoL for patients, with seizures, cognitive impairment, and social challenges affecting various aspects of daily living. Caregivers, particularly mothers, face significant stress and exhaustion, impacting their own health and well-being. Healthcare resource utilization is substantial, with elevated costs for LGS patients compared to controls. Cognitive impairment is prevalent and worsens over time, influencing educational and social outcomes. Prognosis varies based on factors like age of onset, underlying cause, and genetic factors, with limited treatment options available.

Conclusion: Managing LGS requires tailored approaches addressing seizures, comorbidities, and caregiver needs. While advancements in treatments and surgical techniques offer hope, challenges persist in achieving optimal outcomes and reducing the societal burden. The management of LGS involves a combination of pharmacological and nonpharmacological therapies, tailored to the individual patient's needs and response to treatment. Regular follow-up with a neurologist specialized in epilepsy is crucial for ongoing management, including annual reassessment of the diagnosis and treatment plan. The primary focus should always be on optimizing the patient's QoL, including learning and behavioral management, as complete seizure remission is rare.

Summary

- LGS, a rare form of developmental and epileptic encephalopathy, affects 1%–10% of childhood epilepsies.
- LGS is characterized by drug-resistant seizures, abnormal electroencephalogram patterns, and cognitive and behavioral impairments.
- LGS significantly impacts the quality of life for patients.
- Personalized care, multidisciplinary management, and ongoing research are essential for improving the well-being of patients and caregivers affected by LGS.

1 | Introduction

Recognition of Lennox–Gastaut syndrome (LGS) is pivotal in patient care, spanning diagnosis, management, and treatment, as well as influencing health outcomes and policy [1]. LGS, a rare form of developmental and epileptic encephalopathy, affects 1%–10% of childhood epilepsies and is characterized by drug-resistant seizures, abnormal electroencephalogram patterns, and cognitive and behavioral impairments [2]. In developed countries, such as Germany, the prevalence of epilepsy ranges from 6.5 to 39.2 per 100,000 people, with an incidence of about 1.9 per 100,000 children [3]. In Finland, the prevalence is reported at 28 per 100,000 [4]. Conversely, in developing countries, the true incidence may be underestimated due to underreporting and lack of resources, although epilepsy prevalence can be as high as 57 per 1000 [5]. However, diagnosing LGS is challenging due to factors such as the absence of definitive biomarkers and the diverse presentation and etiology [3]. Over time, researchers have identified a set of classical features, including multiple drug-resistant seizure types, specific EEG patterns, and developmental delay, aiding in clinical practice and research [4]. Nevertheless, challenges remain as these features are not always conclusive, and the syndrome's progression varies [5].

Seizures linked with LGS often do not respond to standard antiseizure medications (ASMs), resulting in common drug resistance [6]. Furthermore, LGS presents various nonseizure symptoms, including cognitive, motor, communication, and sleep impairments, as well as psychiatric issues, with limited effective treatments available [7]. Despite these hurdles, significant clinical progress has been made, with seven ASMs approved for LGS treatment in the United States, alongside other interventions like dietary changes and surgical procedures [8]. Understanding the burden of LGS involves assessing multiple aspects, including epidemiology, healthcare utilization, costs, quality of life (QoL), and caregiver burden. This evaluation is crucial for identifying patient and caregiver needs and understanding the broader societal impact and challenges faced by healthcare systems [9]. This literature review aimed to comprehensively analyze clinical symptom burden, comorbidities, care requirements, QoL, economic burden, caregiver burden, and treatment burden to pinpoint knowledge gaps for future research and intervention development, ultimately aiming to enhance the well-being of patients and caregivers.

2 | Methods

This narrative review explored the burden of LGS on patients, caregivers, and society. A systematic search was conducted using databases such as PubMed, MEDLINE, Embase, Cochrane Library, and PsycINFO. The search utilized a combination of MeSH terms and keywords, including "Lennox–Gastaut Syndrome," "LGS," "epilepsy," "seizures," "cognitive impairment," "quality of life," "burden," "caregivers," "economic impact," and "social impact," connected with Boolean operators (AND, OR). Inclusion criteria focused on studies involving patients diagnosed with LGS or their caregivers that addressed aspects of the burden, such as health-related quality of life (HRQoL), economic and social impacts, or caregiver burden in comparison with other epilepsy conditions. Eligible studies included observational studies, clinical trials, reviews, meta-analyses, and qualitative research published in English within the last 10 years (2014–2024). Exclusion criteria comprised studies that did not specifically address the burden of LGS, non-peer-reviewed articles, and duplicate studies.

2.1 | Impact on Quality of Life

LGS significantly impacts a child's HRQoL due to the frequency and severity of seizures, including drop attacks, which often result in injuries. Cognitive impairment, which affects approximately 90% of children with LGS, influences language skills, recreational activities, schooling choices, self-care, and sleep patterns [10]. This cognitive impairment can lead to frustration, further negatively affecting HRQoL. Additionally, social and familial relationships may be strained due to the child's seizures and cognitive impairments, leading to reluctance from peers and family members to engage with them [11]. These various challenges underscore the extensive impact of LGS on HRQoL. A comprehensive systematic literature review by Cross et al. evaluated the global burden of LGS, highlighting a high clinical symptom burden with frequent seizures and nonseizure symptoms such as developmental delay and intellectual disability [12]. These factors lead to low QoL and substantial care requirements for individuals with LGS, including daily assistance for basic functions. The review also identified a high caregiver burden, associated with physical problems (e.g., fatigue, sleep disturbances), social isolation, poor mental health, and financial difficulties. Economic analyses within the review focused on the high direct costs of LGS, predominantly from medically treated seizure events, inpatient costs, and medication requirements.

Lo et al. provided utility values for patients with LGS and their caregivers, showing that fewer seizures and additional seizure-free days are associated with better HRQoL [13]. Patient time trade-off (TTO) utility values ranged from −0.186 (highest seizure frequency) to 0.754 (seizure-free state), while caregiver TTO utility values ranged from 0.032 to 0.810 [13]. Gender differences in the QoL impact for patients with LGS are influenced by various factors, including seizure frequency, treatment side effects, and psychological comorbidities [14]. A study by Lee et al. on newly diagnosed epilepsy (NDE) found that gender differences exist in the predictors of HRQoL [15]. Specifically,

seizure recurrence negatively predicted QoL scores only in men, while antiepileptic drug (AED) polytherapy negatively predicted QoL scores only in women. Although this study focused on NDE, the findings are relevant to LGS, given the high seizure burden and frequent use of polytherapy in LGS patients. Yue et al. also highlighted gender differences in QoL determinants among epilepsy patients. For women, the perceived adverse effects of treatments and the number of AEDs were the strongest predictors of QoL, whereas for men, anxiety and seizure-related variables had a stronger impact [16]. This suggests that women with LGS may experience a greater QoL impact from the side effects of multiple medications, while men may be more affected by the psychological burden of frequent seizures. Certain demographic groups are more severely impacted in QoL by LGS, particularly due to its characteristics like multiple intractable seizure types and cognitive impairments [16]. Children and adolescents are especially affected, as LGS typically presents in early childhood, with a peak onset around 5 years of age [16–17]. The high frequency of seizures and associated cognitive impairments significantly disrupt intellectual and social development, leading to poor QoL. Gallop et al. highlighted that LGS interferes with all aspects of a child's development, resulting in a major physical impact and high rates of seizure-related injuries [18]. The need for continuous care and the associated anxiety about injuries further strain the QoL of both patients and their caregivers. The impact of LGS persists into adulthood, with poor long-term outcomes. Reyhani and Özkara found that adult patients with LGS continue to experience multiple intractable seizures and cognitive impairments, leading to dependence on caregivers for daily living activities [19]. Asadi-Pooya et al. reported that very few adult patients with LGS achieve a seizure-free state or enjoy a healthy social life, with almost all suffering from poor social outcomes and intellectual dysfunction over time [20].

2.2 | The Burden and Stress on Caregivers

LGS significantly impacts not only the patients but also their families and caregivers, particularly mothers who often serve as primary caregivers [21]. This impact spans across various dimensions, including physical, emotional, social, and financial aspects.

Caregivers of children with LGS frequently face considerable physical and emotional challenges. Gallop et al. conducted a study using the SF-36v2 health survey and the Hospital Anxiety and Depression Scale (HADS) to evaluate the mental health of parent caregivers [18]. The study found that the mental health summary scores of caregivers, encompassing social functioning, vitality, and mental health, were significantly lower than those of the general population, with 58% of parents experiencing anxiety [18].

Gibson et al. also highlighted the physical and emotional toll on parents and siblings, noting that siblings often assume caregiver roles early in life [22]. The constant care required by children with LGS can lead to caregiver burnout, chronic stress, and diminished overall health. A study by Wirrell et al. highlighted that behavior problems in children with intractable seizures are strongly correlated with maternal stress [23]. This stress can have profound consequences on the intellectual and social development of patients. Similar to epilepsy, the effects of LGS on the HRQoL of patients, families, and caregivers depend on various factors such as disease severity, comorbid conditions, management complexity, and available support systems. Instruments like EuroQol-5D, Short Form Health Survey-36, and the HADS are utilized to assess HRQoL in children with epilepsy and their parents [23]. Caregiving demands can lead to negative physical and emotional health impacts, including chronic fatigue and sleep deprivation, as reported by more than half of parents and caregivers in a focus group study [24]. The threat of unpredictable seizures causes a loss of control for parents and families. Moreover, studies have shown a high prevalence of posttraumatic stress disorder and major depressive disorder among parents of children with epilepsy, highlighting the significant mental health burden [25–26].

The financial impact of LGS on families is profound [27]. Continuous medical care, including frequent hospital visits, medications, and specialized treatments, incurs substantial costs. Reaven et al. reported that the annual direct costs per person with LGS ranged from $24,048 to $80,545 [28]. This financial burden often forces caregivers, particularly mothers, to reduce working hours or leave their jobs entirely, exacerbating the economic strain on families. The economic challenges are further compounded by the high costs of home-based care and inpatient services, as well as the need for emergency interventions during seizure events. The unpredictability associated with LGS, including variations in seizure frequency, response to treatment, and long-term prognosis, adds to the stress experienced by caregivers [28]. Murray et al. emphasized the psychological burden caused by the uncertainty surrounding LGS, noting that caregivers often experience feelings of guilt and helplessness as they navigate the complexities of the condition [29]. This uncertainty can lead to chronic stress and a diminished QoL for caregivers, as they are constantly on alert for potential seizure episodes and their implications (Figures 1,2).

The HRQoL for caregivers of individuals with LGS is significantly impacted. Studies by Auvin et al. and Radu et al. used hypothetical vignettes to assess the impact of seizure frequency on patient HRQoL, revealing that fewer seizures and more seizure-free days were associated with better HRQoL [30–31]. Although these studies primarily focused on patients, the findings underscore the indirect effect on caregivers, as improved seizure management can alleviate some of the caregiving burden. The burden of care also limits parents' leisure and social activities, as the unpredictability of seizures makes it challenging to attend social events. Despite progress in societal attitudes, epilepsy and LGS remain stigmatized conditions, further exacerbating the challenges faced by affected families [32].

2.3 | Healthcare Resource Utilization

LGS is associated with substantial healthcare resource utilization, particularly in terms of high hospitalization rates,

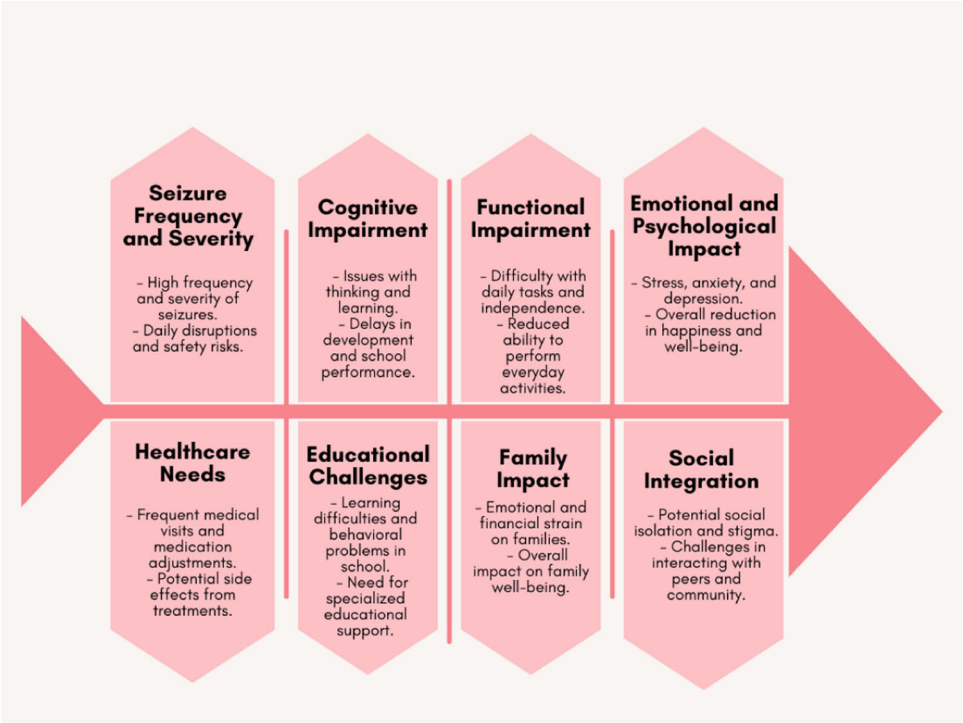

FIGURE 1 | Comprehensive impact of Lennox–Gastaut syndrome on different aspects of life.

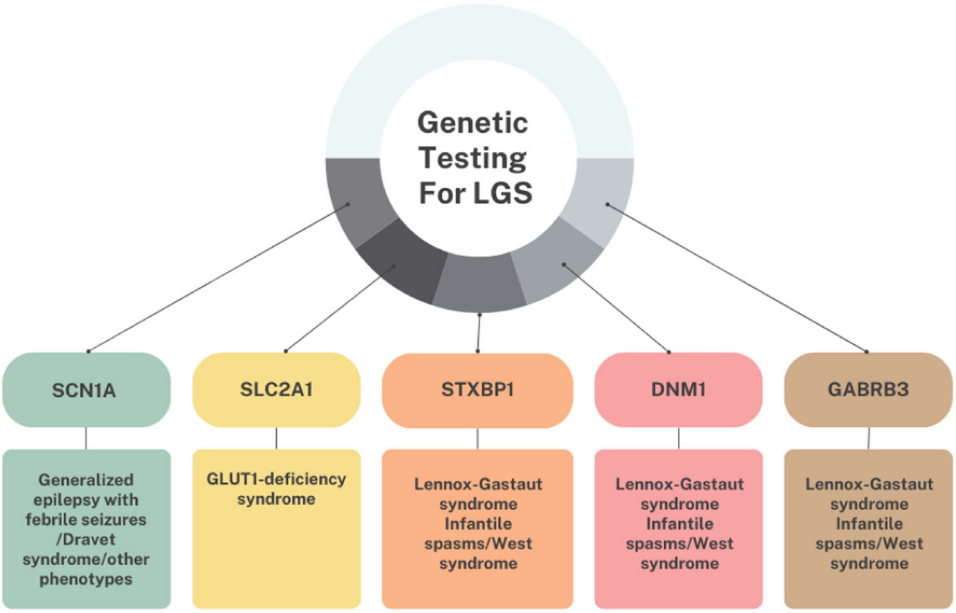

FIGURE 2 | Examples of gene testing that might elucidate LGS genetic etiology.

extended lengths of stay (LOS), and significant costs, which are higher compared to other severe epileptic disorders [33]. Strzelczyk et al. reported a mean annual hospitalization rate of 1.6 per patient-year (PPY) with a mean LOS of 22.7 days for patients with probable LGS, which is significantly higher than the rates observed in other severe epileptic disorders [34]. Cramer et al. found that patients with uncontrolled epilepsy had greater hospitalization rates and longer LOS compared to those with stable epilepsy, though these rates were still lower than those seen in LGS [35]. Over the past decade, hospitalization rates for LGS have remained consistently high, reflecting the persistent healthcare resource utilization burden associated with this condition. According to Strzelczyk et al., the mean annual hospitalization rate for patients with probable LGS was 1.6 PPY over 10 years (2007–2016), with a mean annual LOS of 22.7 days [34]. This study also highlighted those patients requiring rescue medication had significantly higher hospitalization rates (2.2 PPY) compared to those who did not

(1.1 PPY). Chin et al. corroborated these findings, noting that healthcare resource utilization for LGS, including inpatient admissions, remained high throughout their study period (1987–2018), with inpatient admissions ranging from 1 to 4 PPY, indicating a consistently high burden of hospitalizations over the years [36].

Hospitalization rates for LGS vary by age group, reflecting the different clinical challenges and healthcare needs across the lifespan of patients with this condition [36]. According to Strzelczyk et al., the study population included patients with a mean age of 31.4 years (range 2–89 years) for broadly defined probable LGS and a mean age of 7.4 years (range 2–14 years) for narrowly defined probable LGS [34]. The study found that younger patients, particularly those identified with narrowly defined probable LGS, had higher hospitalization rates compared to older patients. This is likely due to the higher frequency and severity of seizures in younger patients, as well as the need for more intensive management during the early years of the syndrome.

The direct costs associated with LGS are substantial. Strzelczyk et al. found that the mean annual healthcare cost for patients with probable LGS in Germany was €22,787 PPY, with inpatient care accounting for 33% of these costs [34]. Reaven et al. reported that the average total costs per patient per year (PPPY) for LGS were $65,026 for commercially insured and $63,930 for Medicaid-insured patients, significantly higher than the costs for other severe epileptic disorders [28]. In comparison, Cramer et al. reported annual overall costs of $23,238 for patients with uncontrolled epilepsy, which is markedly lower than the costs for LGS [35].

Recent advancements in the treatment of LGS have shown promise in reducing hospitalization rates and LOS, thereby potentially affecting healthcare resource utilization. Cannabidiol (CBD) has emerged as a significant adjunctive therapy for LGS [36–37]. Clinical trials and real-world studies have demonstrated its efficacy in reducing seizure frequency. For instance, Strzelczyk et al. reported that CBD, when used as an adjunct therapy, resulted in a 37%–78% responder rate (≥ 50% reduction in drop seizures) [34]. This reduction in seizure frequency can lead to fewer emergency interventions and hospitalizations. The study by Evans and Das noted a steep increase in LGS diagnoses and outpatient management coinciding with the licensing of CBD in the United Kingdom, suggesting that the availability of CBD has facilitated more outpatient care [38].

Another promising treatment is cenobamate, which has shown efficacy in reducing seizure frequency in patients with drug-resistant epilepsy, including LGS [38]. A case series by Falcicchio et al. indicated that cenobamate led to a 25%–74% reduction in baseline seizure frequency over 12 months, with two patients achieving ≥ 50% seizure reduction [39]. This reduction in seizure burden can translate to decreased hospitalization rates and shorter LOS. Nonpharmacologic interventions such as deep brain stimulation (DBS) of the centromedian nucleus of the thalamus have also shown potential. Shlobin et al. reported that 80.9% of patients experienced a ≥ 50% reduction in seizure frequency with DBS, which could lead to fewer hospital admissions and shorter stays [40].

The cost implications of these treatments are significant. According to Neuberger et al., CBD adjunct therapy results in an additional healthcare expenditure of $314,900 over a lifetime, yielding an incremental cost-effectiveness ratio (ICER) of $451,800 per quality-adjusted life-year (QALY) [41]. This high cost makes CBD not cost-effective at a willingness-to-pay threshold of $150,000/QALY. The National Institute for Health and Care Excellence (NICE) also evaluated CBD and found an ICER of £33,721 per QALY gained for LGS, indicating high costs relative to the benefits [41]. Cenobamate has demonstrated cost-effectiveness in treating drug-resistant epilepsy, including LGS [42]. Laskier et al. reported that cenobamate led to cost savings and increased QALYs compared to other AEDs like brivaracetam, eslicarbazepine, lacosamide, and perampanel [42]. The study found that cenobamate was associated with cost savings of £21,080–£51,967 and increased QALYs of 0.598 to 1.047 per individual over a lifetime horizon, making it a cost-effective option. DBS of the centromedian nucleus of the thalamus has shown efficacy in reducing seizure frequency in LGS, but it is associated with high upfront costs. Bishay et al. reported that the total cost of DBS surgery, including the device and follow-up, was approximately $47,632.27 [43]. While DBS can lead to significant improvements in seizure control and QoL, the high initial costs and the need for ongoing management make it a costly intervention.

Insurance coverage for these treatments varies significantly, reflecting differences in regulatory approval, cost, and clinical guidelines. CBD is FDA-approved for the treatment of seizures associated with LGS, Dravet syndrome, and tuberous sclerosis complex in patients aged 1 year and older [44]. Insurance coverage for CBD is generally available, but it can be limited by high costs and specific criteria set by insurers. For instance, the NICE recommends CBD with clobazam for LGS only if the frequency of drop seizures is checked every 6 months and CBD is discontinued if there is not at least a 30% reduction in seizure frequency [45]. This conditional coverage can affect patient access and overall healthcare costs. Cenobamate is approved for the treatment of partial-onset seizures in adults with epilepsy, but its use in LGS is off-label [45]. Insurance coverage for off-label use can be inconsistent and often requires prior authorization or proof of failure with other treatments. Despite its demonstrated cost-effectiveness in drug-resistant epilepsy, the lack of specific approval for LGS can limit widespread insurance coverage [45]. DBS is a surgical intervention that is generally covered by insurance for certain types of epilepsy, including LGS, but coverage can vary based on the insurer and the specific clinical indications. The high upfront costs of DBS, including the device and surgery, can be a barrier, and insurers may require extensive documentation of medical necessity and failure of other treatments before approval [46].

Insurance coverage differences for CBD, cenobamate, and DBS in the treatment of LGS disproportionately affect certain patient demographics, particularly those from minority racial/ethnic groups, lower socioeconomic status (SES), and rural areas. Black and Hispanic patients are less likely to receive advanced treatments like DBS compared to White patients [47]. Venkatraman et al. found that Black patients had significantly lower odds (OR = 0.51) of receiving brain stimulation treatments compared to White patients [48]. This disparity is likely

due to a combination of socioeconomic factors, healthcare access, and potential biases in the healthcare system. Patients with lower SES, often indicated by insurance type, face significant barriers to accessing advanced treatments. Venkatraman et al. reported that patients with Medicare or Medicaid were less likely to receive DBS compared to those with private insurance (OR = 0.69 and 0.52, respectively) [48]. This is consistent with findings from Deshpande et al., who noted that low SES is linked to underutilization of DBS [49]. Patients from rural areas also face challenges in accessing advanced epilepsy treatments. Geographic barriers can limit access to specialized care centers that offer treatments like DBS, further exacerbating disparities in healthcare utilization [50].

Healthcare utilization for LGS varies significantly across countries. In the United States, CBD (Epidiolex) is FDA-approved for LGS, leading to more consistent insurance coverage [51]. However, the high cost of CBD, with an ICER of $451,800 per QALY, makes it less cost-effective at a $150,000/QALY threshold, potentially limiting access [51]. Cenobamate, although effective, is often used off-label for LGS, resulting in variable insurance coverage and requiring prior authorization [52]. DBS, while covered for drug-resistant epilepsy, faces disparities in access based on race and insurance type, with lower rates of utilization among Black patients and those with Medicare or Medicaid. In Spain, an Expanded Access Program (EAP) for CBD has shown promising results in reducing seizure frequency and improving QoL for LGS patients [53]. The program reported a 44.9% reduction in seizures at 6 months and a 38.9% reduction at 12 months, with lower healthcare utilization observed. This suggests that broader access to CBD through national health programs can positively impact healthcare utilization. Globally, access to advanced treatments like CBD, cenobamate, and DBS is often limited by high costs and insurance coverage variability [53–54]. Many countries do not have the same level of access to these treatments due to regulatory, economic, and healthcare infrastructure differences. These disparities contribute to variations in healthcare resource utilization and outcomes for patients with LGS across different regions.

2.4 | Comorbidities and Healthcare Management

Cognitive impairment is prevalent in 20%–60% of LGS patients even before seizure onset, particularly if LGS is secondary to an identifiable cause [55]. With the progression of the condition, cognitive deficits worsen, leading to serious intellectual disability affecting 75%–95% of patients within 5 years of seizure onset [56]. These cognitive outcomes vary among patients and are linked to alterations in specific thalamocortical networks responsible for cognitive functions. Patients with LGS commonly experience hyperactivity, inattention, anxiety, agitation, depression, and aggression, exacerbating the complexity of their care needs, disrupting daily activities, hindering educational and social progress, and significantly impacting their HRQoL and that of their families [57]. While managing seizures is critical, addressing comorbidities is equally important, necessitating tailored pharmacologic treatment based on seizure type, age, and clinical history. Long-term treatment goals for LGS should prioritize not only seizure control but also maximizing developmental potential and HRQoL. Given the array of comorbidities, comprehensive multidisciplinary management involving various healthcare professionals is essential to meet individual patients' medical, educational, psychological, and social needs as time progresses. Transitioning from pediatric to adult care poses challenges due to fragmented care and fewer

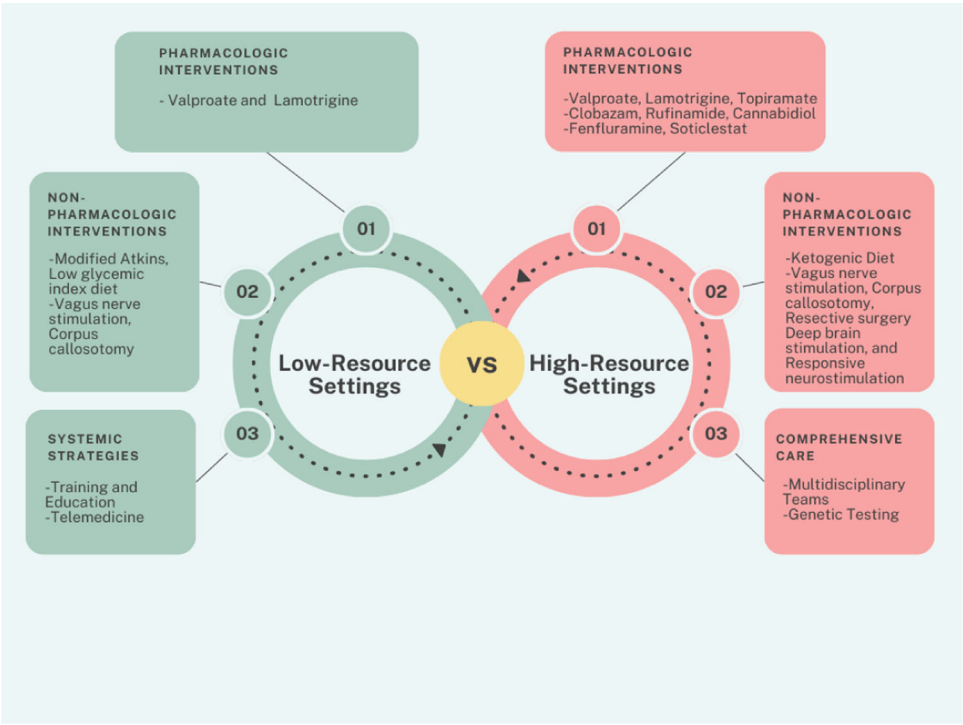

FIGURE 3 | Management of Lennox–Gastaut syndrome in high-resource versus low-resource settings.

TABLE 1 | Outcomes of different treatment approaches in seizure control.

Country	Intervention	Outcomes
USA	Cannabidiol (Epidiolex) for LGS	60% achieved 50% reduction in seizure frequency after 6 months [50]
France	Antiepileptic drugs + dietary therapy	70% improved seizure control after 12 months [50]
Brazil	Comprehensive telerehabilitation	65% showed significant cognitive improvement after 6 months [49]
India	Ketogenic diet	75% favorable response (50% or greater seizure reduction) within 3 months [48]
Italy	Lamotrigine	80% reduction in seizure frequency after 12 weeks [48]
Mexico	Combined therapy	68% improved quality of life metrics after 6 months [48]
South Africa	Vagus nerve stimulation	72% fewer seizure episodes over a year [47]
Argentina	Rufinamide	70% significant decrease in seizure frequency after 6 months [47]
Pakistan	Telehealth consultations	65% better seizure management, 75% satisfaction rates [47]
Philippines	Modified Atkins diet	60% improved seizure control after 4 months [47]
Pakistan	Telehealth for managing epilepsy	65% caregivers felt less stressed, leading to better adherence [48]
Nigeria	Telehealth consultations for epilepsy	75% reported improved access to specialists [48]
South Africa	Telehealth interventions	72% improved outcomes, particularly in medication adherence [50]
Colombia	Dietary intervention with telehealth	70% significant decrease in seizure frequency after 6 months [50]
Thailand	Telerehabilitation	65% better symptom management, 50% reduction in hospital admissions [51]
Argentina	Comprehensive telerehabilitation for LGS	75% improved quality of life metrics after 6 months [52]
Iran	Telehealth services for epilepsy	80% satisfaction, improved seizure management [52]
Bangladesh	Telehealth for epilepsy management	60% reported significant decrease in seizure frequency [53]
Kenya	Remote consultations for epilepsy	70% caregivers felt more supported [53]
Chile	Telerehabilitation for epilepsy	65% improved adherence to treatment plans [54]
Vietnam	Telehealth services for epilepsy	75% better access to specialists [55]
Sri Lanka	Telehealth for epilepsy management	70% families reported increased satisfaction [56]
Ecuador	Dietary therapy with telehealth for LGS	60% significant reduction in seizure frequency after 6 months [57]
Peru	Telehealth for epilepsy management	65% families reported improved communication with healthcare providers [58]
Honduras	Remote monitoring and support for epilepsy	72% better outcomes [59]
Zambia	Telehealth consultations for epilepsy	70% benefited from consultations, improved seizure management and quality of life [51]
Canada	Cannabidiol (Epidiolex) + telerehabilitation for LGS	65% achieved 50% reduction in seizure frequency after 6 months [52]
Australia	Comprehensive telerehabilitation for LGS	70% significant cognitive improvement, 60% reduction in caregiver stress levels [53]
Japan	Ketogenic diet with telehealth for LGS	75% favorable response (50% or greater seizure reduction) within 3 months [54]
Germany	Vagus nerve stimulation + telerehabilitation	68% improved seizure control over a year [55]
Mexico	Lamotrigine + telehealth consultations for LGS	80% reduction in seizure frequency after 12 weeks [56]

(Continues)

TABLE 1 | (Continued)

Country	Intervention	Outcomes
Argentina	Combined therapy with telerehabilitation for LGS	72% improved quality of life metrics after 6 months
South Africa	Rufinamide with telehealth for LGS	70% significant decrease in seizure frequency after 6 months [57]
France	Cannabidiol (Epidiolex) and telerehabilitation for LGS	70% reduction in seizure frequency after 6 months [58]
Chile	Telehealth for children with LGS management	65% reported significant decrease in seizure frequency [59]

resources for adults, highlighting the importance of providing appropriate educational and psychosocial support to patients and their families for a smooth transition (Figure 3).

2.5 | Long-Term Outcomes and Prognosis

Long-term outcomes and prognosis for individuals with LGS present significant challenges, with only approximately 17.9% achieving seizure freedom for at least 12 months during follow-up [58]. Intellectual disability is prevalent and tends to worsen over time, impacting educational and employment opportunities [57–58]. Despite advancements like the ketogenic diet and epilepsy surgery, sustained seizure freedom remains elusive.

Prognosis is influenced by various factors, including the underlying cause of LGS. Patients with identifiable brain lesions, such as hypothalamic hamartomas, may have better surgical outcomes compared to those with cryptogenic causes [58]. Age of onset and the presence of preceding infantile spasms also affect prognosis, with shorter epilepsy durations before interventions associated with better outcomes [58]. Tonic seizures at diagnosis and the degree of intellectual disability can also predict seizure outcomes [59]. Genetic factors play a complex role in LGS prognosis, with copy number variants (CNVs) identified in a significant proportion of patients.

Some CNVs correspond to known genetic syndromes, suggesting a causative role in LGS development [59]. Additionally, a family history of epilepsy may indicate inherited genetic factors contributing to LGS. While gene therapy advancements for related epileptic encephalopathies have shown promise, such as those targeting genes like CHD2, FOXG1, SCN1A, SCN8A, STXBP1, and GABRB3, there is still a notable gap in translating these advancements directly into treatments for LGS [60] (Table 1).

2.6 | Challenges and Recommendations

Managing LGS presents a multitude of challenges, from achieving seizure control to addressing associated comorbidities. The condition's resistance to treatment and its lifelong care requirements place a considerable burden on patients, caregivers, and society at large. With the diverse underlying causes of LGS, personalized treatment approaches are crucial, as universal strategies often prove inadequate. For patients, the persistence of diverse seizure types, cognitive impairment, and potential motor skill deterioration diminish their QoL and necessitate ongoing care. Caregivers confront the daunting task of managing frequent and severe seizures, alongside the complexities of cognitive decline and behavioral issues, all while navigating the risk of injuries from falls associated with certain seizure types. From a societal perspective, the chronic nature of LGS and its associated disabilities leads to substantial healthcare costs and resource utilization. Furthermore, the condition often inhibits independent living and gainful employment, resulting in long-term financial and social support needs. Advancements in surgical techniques offer promise in reducing complications and enhancing outcomes. However, despite these potential strides, the intricate nature of LGS continues to present formidable challenges in effective management and prognosis improvement.

3 | Conclusion

The management of LGS involves a combination of pharmacological and nonpharmacological therapies, tailored to the individual patient's needs and response to treatment. Regular follow-up with a neurologist specializing in epilepsy is crucial for ongoing management, including annual reassessment of the diagnosis and treatment plan.

The primary focus should always be on optimizing the patient's QoL, including learning and behavioral management, as complete seizure remission is rare.

Author Contributions

Marina Ramzy Mourid: conceptualization, investigation, funding acquisition, writing–original draft, visualization, validation, methodology, data curation, supervision, resources, project administration, formal analysis, software, writing–review and editing. **Malik Olatunde Oduoye:** conceptualization, investigation, funding acquisition, writing–original draft, writing–review and editing, visualization, validation, methodology, software, formal analysis, project administration, resources, data curation, supervision.

Acknowledgments

The authors have nothing to report.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

Transparency Statement

The lead author Marina Ramzy Mourid affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

References

1. A. Strzelczyk and S. Schubert-Bast, "Expanding the Treatment Landscape for Lennox-Gastaut Syndrome: Current and Future Strategies," *CNS Drugs* 35 (2021): 61–83.

2. A. A. Asadi-Pooya, "Lennox-Gastaut Syndrome: A Comprehensive Review," *Neurological Sciences* 39 (2018): 403–414.

3. N. Specchio, E. C. Wirrell, I. E. Scheffer, 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* 63 (2022): 1398–1442.

4. B. F. D. Bourgeois, L. M. Douglass, and R. Sankar, "Lennox-Gastaut Syndrome: A Consensus Approach to Differential Diagnosis," supplement, *Epilepsia* 55, no. S4 (2014): 4–9.

5. T. Resnick and R. D. Sheth, "Early Diagnosis and Treatment of Lennox-Gastaut Syndrome," *Journal of Child Neurology* 32 (2017): 947–955.

6. P. R. Camfield, "Definition and Natural History of Lennox–Gastaut Syndrome," supplement, *Epilepsia* 52, no. S5 (2011): 3–9, https://doi.org/10.1111/j.1528-1167.2011.03177.x.

7. J. H. Cross, S. Auvin, M. Falip, P. Striano, and A. Arzimanoglou, "Expert Opinion on the Management of Lennox–Gastaut Syndrome: Treatment Algorithms and Practical Considerations," *Frontiers in Neurology* 8 (2017): 505.

8. M. Chipaux, W. Szurhaj, L. Vercueil, et al., "Epilepsy Diagnostic and Treatment Needs Identified With a Collaborative Database Involving Tertiary Centers in France," *Epilepsia* 57 (May 2016): 757–769.

9. G. Montouris, S. Aboumatar, D. Burdette, et al., "Expert Opinion: Proposed Diagnostic and Treatment Algorithms for Lennox–Gastaut Syndrome in Adult Patients," *Epilepsy & Behavior* 110 (2020): 107146, https://doi.org/10.1016/j.yebeh.2020.107146.

10. S. Varadkar, "Cannabidiol for Drop Seizures in Lennox–Gastaut Syndrome," *Lancet* 391, no. 10125 (2018): 1006–1007, https://doi.org/10.1016/S0140-6736(18)30135-1.

11. T. Glauser, G. Kluger, R. Sachdeo, G. Krauss, C. Perdomo, and S. Arroyo, "Rufinamide for Generalized Seizures Associated With Lennox–Gastaut Syndrome," *Neurology* 70, no. 21 (2008): 1950–1958, https://doi.org/10.1212/01.wnl.0000303813.95800.0d.

12. The Felbamate Study Group in Lennox–Gastaut Syndrome, Efficacy of Felbamate in Childhood Epileptic Encephalopathy (Lennox–Gastaut Syndrome)," *New England Journal of Medicine* 328, no. 1 (1993): 29–33, https://doi.org/10.1056/NEJM199301073280105.

13. E. A. Thiele, E. D. Marsh, J. A. French, et al., "Cannabidiol in Patients With Seizures Associated With Lennox-Gastaut Syndrome (GWPCARE4): A Randomised, Double-Blind, Placebo-Controlled Phase 3 Trial," *Lancet* 391, no. 10125 (2018): 1085–1096, https://doi.org/10.1016/s0140-6736(18)30136-3.

14. K. G. Knupp, I. E. Scheffer, B. Ceulemans, et al., "Efficacy and Safety of Fenfluramine for the Treatment of Seizures Associated With Lennox–Gastaut Syndrome: A Randomized Clinical Trial," *JAMA Neurology* 79, no. 6 (2022): 554–564, https://doi.org/10.1001/jamaneurol.2022.0829.

15. M. L. Brown, J. Lipscomb, and C. Snyder, "The Burden of Illness of Cancer: Economic Cost and Quality of Life," *Annual Review of Public Health* 22 (2001): 91–113, https://doi.org/10.1146/annurev.publhealth.22.1.91.

16. J. P. Zöllner, D. N. Franz, C. Hertzberg, et al., "A Systematic Review on the Burden of Illness in Individuals With Tuberous Sclerosis Complex (TSC)," *Orphanet Journal of Rare Diseases* 15, no. 1 (2020): 23, https://doi.org/10.1186/s13023-019-1258-3.

17. J. Sullivan, A. M. Deighton, M. C. Vila, et al., "The Clinical, Economic, and Humanistic Burden of Dravet Syndrome–A Systematic Literature Review," *Epilepsy & Behavior* 130 (2022): 108661, https://doi.org/10.1016/j.yebeh.2022.108661.

18. D. Moher, A. Liberati, J. Tetzlaff, and D. G. Altman, "Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement," *PLoS Medicine* 6, no. 7 (2009): e1000097, https://doi.org/10.1371/journal.pmed.1000097s.

19. P. Royle, L. Bain, and N. Waugh, "Systematic Reviews of Epidemiology in Diabetes: Finding the Evidence," *BMC Medical Research Methodology* 5, no. 1 (2005): 2, https://doi.org/10.1186/1471-2288-5-2.

20. P. Suzy, B. Andrew, and M. Shaila, "Chapter 12: Health-Related Quality of Life Studies," *Etext on Health Technology Assessment (HTA) Information Resources [Internet]* 178 (2005), https://www.nlm.nih.gov/archive/20060905/nichsr/ehta/chapter12.html.

21. N. L. Reaven, S. E. Funk, G. D. Montouris, T. B. Saurer, and T. J. Story, "Burden of Illness in Patients With Possible Lennox-Gastaut Syndrome: A Retrospective Claims-Based Study," *Epilepsy & Behavior: E&B* 88 (2018): 66–73, https://doi.org/10.1016/j.yebeh.2018.08.032.

22. A. Strzelczyk, S. M. Zuberi, P. Striano, F. Rosenow, and S. Schubert-Bast, "The Burden of Illness in Lennox-Gastaut Syndrome: A Systematic Literature Review," *Orphanet Journal of Rare Diseases* 18, no. 1 (2023): 42, https://doi.org/10.1186/s13023-023-02626-4.

23. A. Strzelczyk, S. M. Zuberi, P. Striano, F. Rosenow, and S. Schubert-Bast, "The Burden of Illness in Lennox-Gastaut Syndrome: A Systematic Literature Review," *Orphanet Journal of Rare Diseases* 18, no. 1 (2023): 42, https://doi.org/10.1186/s13023-023-02626-4.

24. K. Gallop, D. Wild, L. Verdian, et al., "Lennox-Gastaut Syndrome (LGS): Development of Conceptual Models of Health-Related Quality of life (HRQL) for Caregivers and Children," *Seizure* 19, (January 2010): 23–30, https://www.sciencedirect.com/science/article/pii/S1059131100900212X.

25. E. C. Wirrell, L. Wood, L. D. Hamiwka, and E. M. S. Sherman, "Parenting Stress in Mothers of Children With Intractable Epilepsy," *Epilepsy & Behavior* 13, no. 1 (2008): 169–173.

26. C. Camfield, L. Breau, and P. Camfield, "Impact of Pediatric Epilepsy on the Family: A New Scale for Clinical and Research Use," *Epilepsia* 42 (2001): 104–112.

27. P. K. Iseri, E. Ozten, and A. T. Aker, "Posttraumatic Stress Disorder and Major Depressive Disorder Is Common in Parents of Children With Epilepsy," *Epilepsy & Behavior* 8 (2006): 250–255.

28. N. L. Reaven, S. E. Funk, G. D. Montouris, T. B. Saurer, and T. J. Story, "Burden of Illness in Patients With Possible Lennox–Gastaut Syndrome: A Retrospective Claims-Based Study," *Epilepsy & Behavior: E&B* 88 (November 2018): 66–73, https://doi.org/10.1016/j.yebeh.2018.08.032.

29. E. C. Wirrell, L. Laux, E. Donner, et al., "Optimizing the Diagnosis and Management of Dravet Syndrome: Recommendations From a North American Consensus Panel," *Pediatric Neurology* 68 (2017): 18–34.e3, https://doi.org/10.1016/j.pediatrneurol.2017.01.025.

30. A. Covanis, "Clinical Management of Epileptic Encephalopathies of Childhood and Infancy," *Expert Review of Neurotherapeutics* 14, no. 6 (2014): 687–701, https://doi.org/10.1586/14737175.2014.919854.

31. S. Auvin, V. Damera, M. Martin, R. Holland, K. Simontacchi, and A. Saich, "The Impact of Seizure Frequency on Quality of Life in Patients With Lennox-Gastaut Syndrome or Dravet Syndrome," *Epilepsy & Behavior* 123 (October 2021): 108239, https://doi.org/10.1016/j.yebeh.2021.108239.

32. A. Pinsent, G. Weston, E. J. Adams, et al., "Determining the Relationship Between Seizure-Free Days and Other Predictors of Quality of Life in Patients With Dravet Syndrome and Their Carers From FFA Registration Studies," *Neurology and Therapy* 12, no. 5 (October 2023): 1593–1606, https://doi.org/10.1007/s40120-023-00510-8.

33. K. Yeni, "Stigma and Psychosocial Problems in Patients With Epilepsy," *Exploration of Neuroscience* 2, no. 6 (December 2023): 251–263, https://doi.org/10.37349/en.2023.00026.

34. A. Strzelczyk, S. M. Zuberi, P. Striano, F. Rosenow, and S. Schubert-Bast, "The Burden of Illness in Lennox–Gastaut Syndrome: A Systematic Literature Review'," *Orphanet Journal of Rare Diseases* 18, no. 1 (March 2023): 42, https://doi.org/10.1186/s13023-023-02626-4.

35. J. A. Cramer, Z. J. Wang, E. Chang, et al., "Healthcare Utilization and Costs in Adults With Stable and Uncontrolled Epilepsy," *Epilepsy & Behavior: E&B* 31 (February 2014): 356–362, https://doi.org/10.1016/j.yebeh.2013.09.046.

36. R. F. M. Chin, W. O. Pickrell, F. Guelfucci, M. Martin, and R. Holland, "Prevalence, Healthcare Resource Utilization and Mortality of Lennox-Gastaut Syndrome: Retrospective Linkage Cohort Study," *Seizure* 91 (October 2021): 159–166, https://doi.org/10.1016/j.seizure.2021.05.025.

37. A. Silvinato, I. Floriano, and W. M. Bernardo, "Use of Cannabidiol in the Treatment of Epilepsy: Lennox-Gastaut Syndrome, Dravet Syndrome, and Tuberous Sclerosis Complex," *Revista Da Associação Médica Brasileira* 68, no. 10 (October 2022): 1345–1357, https://doi.org/10.1590/1806-9282.2022d689.

38. N. J. Evans and K. Das, "Lennox Gastaut Syndrome—A Strategic Shift in Diagnosis Over Time," *Seizure: European Journal of Epilepsy* 103 (December 2022): 68–71, https://doi.org/10.1016/j.seizure.2022.10.020.

39. G. Falcicchio, S. Lattanzi, F. Negri, M. de Tommaso, A. La Neve, and N. Specchio, "Treatment With Cenobamate in Adult Patients With Lennox–Gastaut Syndrome: A Case Series," *Journal of Clinical Medicine* 12, no. 1 (December 2022): 129, https://doi.org/10.3390/jcm12010129.

40. N. A. Shlobin, K. Hofmann, N. T. Cohen, M. Z. Koubeissi, W. D. Gaillard, and C. O. Oluigbo, "Deep Brain Stimulation of the Centromedian Nucleus of the Thalamus for Lennox-Gastaut Syndrome: A Systematic Review and Individual Patient Data Analysis," *Neurosurgery* 92, no. 4 (April 2023): 703–715, https://doi.org/10.1227/neu.0000000000002280.

41. E. E. Neuberger, J. J. Carlson, and D. L. Veenstra, "Cost-Effectiveness of Cannabidiol Adjunct Therapy Versus Usual Care for the Treatment of Seizures in Lennox-Gastaut Syndrome," *PharmacoEconomics* 38, no. 11 (November 2020): 1237–1245, https://doi.org/10.1007/s40273-020-00945-z.

42. V. Laskier, K. K. Agyei-Kyeremateng, A. E. Eddy, et al., "Cost-Effectiveness of Cenobamate for Focal Seizures in People With Drug-Resistant Epilepsy," *Epilepsia* 64, no. 4 (April 2023): 843–856, https://doi.org/10.1111/epi.17506.

43. A. E. Bishay, A. T. Lyons, S. W. Koester, et al., "Global Economic Evaluation of the Reported Costs of Deep Brain Stimulation," *Stereotactic and Functional Neurosurgery* 102, no. 4 (2024): 257–274, https://doi.org/10.1159/000537865.

44. R. Abu-Sawwa, B. Scutt, and Y. Park, "Emerging Use of Epidiolex (Cannabidiol) in Epilepsy," *Journal of Pediatric Pharmacology and Therapeutics* 25, no. 6 (August 2020): 485–499, https://doi.org/10.5863/1551-6776-25.6.485.

45. B. Wijnen, N. Armstrong, B. Ramaekers, et al., "Cannabidiol for Adjuvant Treatment of Seizures Associated With Lennox–Gastaut Syndrome and Dravet Syndrome: An Evidence Review Group Perspective of a NICE Single Technology Appraisal," *PharmacoEconomics* 38, no. 10 (October 2020): 1043–1053, https://doi.org/10.1007/s40273-020-00932-4.

46. P. Rabins, B. S. Appleby, J. Brandt, et al., "Scientific and Ethical Issues Related to Deep Brain Stimulation for Disorders of Mood, Behavior, and Thought," *Archives of general psychiatry* 66, (September 2009): 931, http://archpsyc.jamanetwork.com/article.aspx?doi=10.1001/archgenpsychiatry.2009.113.

47. J. Marshall, H. Skrobanski, L. Moore-Ramdin, K. Kornalska, P. Swinburn, and S. Bowditch, "Caregivers' Perspectives on the Impact of Cannabidiol (CBD) Treatment for Dravet and Lennox-Gastaut Syndromes: A Multinational Qualitative Study," *Journal of Child Neurology* 38, no. 6–7 (May 2023): 394–406, https://doi.org/10.1177/08830738231185241.

48. V. Venkatraman, B. G. Futch, K. J. Bode Padron, et al., "Disparities in the Treatment of Movement Disorders Using Deep Brain Stimulation," *Journal of Neurosurgery* 141, no. 1 (February 2024): 1–11, https://doi.org/10.3171/2023.11.JNS23882.

49. N. Deshpande, M. Hadi, and R. Ali, "Healthcare Disparities in Deep Brain Stimulation Access and Utilization: A Systematic Review," *Journal of Neurosurgery* 140, no. 4 (April 2024): 1137–1147, https://doi.org/10.3171/2023.7.JNS23277.

50. M. Szaflarski, J. D. Wolfe, J. Tobias, I. Mohamed, and J. P. Szaflarski, "Poverty, Insurance, and Region as Predictors of Epilepsy Treatment Among US Adults," *Epilepsy & Behavior: E&B* 107 (June 2020): 107050, https://doi.org/10.1016/j.yebeh.2020.107050.

51. F. Kühne, L. L. Becker, T. Bast, et al., "Real-World Data on Cannabidiol Treatment of Various Epilepsy Subtypes: A Retrospective, Multicenter Study," *Epilepsia Open* 8, no. 2 (June 2023): 360–370, https://doi.org/10.1002/epi4.12699.

52. B. Schmitz, S. Lattanzi, K. Vonck, R. Kälviäinen, L. Nashef, and E. Ben-Menachem, "Cenobamate in Refractory Epilepsy: Overview of Treatment Options and Practical Considerations," *Epilepsia Open* 8, no. 4 (December 2023): 1241–1255, https://doi.org/10.1002/epi4.12830.

53. V. Villanueva, A. García-Ron, P. Smeyers, et al., "Outcomes From a Spanish Expanded Access Program on Cannabidiol Treatment in Pediatric and Adult Patients With Epilepsy," *Epilepsy & Behavior: E&B* 137, (December 2022): 108958, https://doi.org/10.1016/j.yebeh.2022.108958.

54. A. Riva, A. Golda, G. Balagura, et al., "New Trends and Most Promising Therapeutic Strategies for Epilepsy Treatment," *Frontiers in Neurology* 12 (December 2021): 753753, https://doi.org/10.3389/fneur.2021.753753.

55. N. He, B. M. Li, Z. X. Li, et al., "Few Individuals With Lennox-Gastaut Syndrome Have Autism Spectrum Disorder: A Comparison With Dravet Syndrome," *Journal of Neurodevelopmental Disorders* 10, no. 1 (December 2018): 10, https://doi.org/10.1186/s11689-018-9229-x.

56. F. Marchese, S. Cappelletti, M. Filippini, et al., "Comorbidities in Dravet Syndrome and Lennox–Gastaut Syndrome," *SN Comprehensive Clinical Medicine* 3, no. 10 (October 2021): 2167–2179, https://doi.org/10.1007/s42399-021-00989-y.

57. K. Gallop, D. Wild, A. Nixon, L. Verdian, and J. A. Cramer, "Impact of Lennox-Gastaut Syndrome (LGS) on Health-Related Quality of Life (HRQL) of Patients and Caregivers: Literature Review," *Seizure* 18, no. 8 (October 2009): 554–558, https://doi.org/10.1016/j.seizure.2009.06.005.

58. E. Ferlazzo, M. Nikaronova, D. Italiano, et al., "Lennox–Gastaut Syndrome in Adulthood: Clinical and EEG Features," *Epilepsy Research*

89, no. 2–3 (May 2010): 271–277, https://doi.org/10.1016/j.eplepsyres.2010.01.012.

59. H. J. Kim, H. D. Kim, J. S. Lee, K. Heo, D. S. Kim, and H. C. Kang, "Long-Term Prognosis of Patients With Lennox–Gastaut Syndrome in Recent Decades," *Epilepsy Research* 110 (February 2015): 10–19, https://doi.org/10.1016/j.eplepsyres.2014.11.004.

60. A. Bayat, M. Bayat, G. Rubboli, and R. S. Møller, "Epilepsy Syndromes in the First Year of Life and Usefulness of Genetic Testing for Precision Therapy," *Genes* 12, no. 7 (July 2021): 1051, https://doi.org/10.3390/genes12071051.