Received: 19 April 2024 | Revised: 25 September 2024 | Accepted: 30 September 2024

DOI: 10.1002/epi4.13075

Epilepsia Open® Open Access

INVITED COMMENTARY

Refining management strategies for Lennox–Gastaut syndrome: Updated algorithms and practical approaches

Stéphane Auvin[1,2,3] | **Alexis Arzimanoglou**[4] | **Mercè Falip**[5] | **Pasquale Striano**[6,7] | **J. Helen Cross**[8]

[1]INSERM NeuroDiderot, Université Paris Cité, Paris, France

[2]Pediatric Neurology Department, CRMR Epilepsies Rares, ERN EpiCare, APHP, Robert Debré University Hospital, Paris, France

[3]Institut Universitaire de France, (IUF), Paris, France

[4]Epilepsy Unit, Child Neurology Department, Hospital San Juan de Déu, Coordinator of the ERN EpiCARE, Universitat de Barcelona, Barcelona, Spain

[5]Epilepsy Unit, Neurology Service, Bellvitge University Hospital, L'Hospitalet de Llobregat, Barcelona, Spain

[6]Department of Neurosciences, Rehabilitation, Ophthalmology, Genetics, Maternal and Child Health, University of Genoa, Genoa, Italy

[7]IRCCS 'G. Gaslini' Institute, ERN EpiCARE, Genoa, Italy

[8]UCL NIHR BRC Great Ormond Street Institute of Child Health, London, UK

Correspondence
Stéphane Auvin, Service de Neurologie Pédiatrique, CHU Hôpital Robert Debré, 48, Boulevard Sérurier, Paris 75935, Cedex 19, France.
Email: stephane.auvin@aphp.fr

Funding information
UCB; Italian Ministry of Health, RICERCA CORRENTE 2024

Abstract

Lennox–Gastaut syndrome (LGS) is a severe developmental and epileptic encephalopathy (DEE) characterized by multiple types of drug-resistant seizures (which must include tonic seizures) with classical onset before 8 years (although some cases with later onset have also been described), abnormal electroencephalographic features, and cognitive and behavioral impairments. Management and treatment of LGS are challenging, due to associated comorbidities and the treatment resistance of seizures. A panel of five epileptologists reconvened to provide updated guidance and treatment algorithms for LGS, incorporating recent advancements in antiseizure medications (ASMs) and understanding of DEEs. The resulting consensus document is based on current evidence from clinical trials and clinical practice and the panel's expert opinion, focusing on new ASMs with novel mechanisms of action, such as highly purified cannabidiol and fenfluramine. For a patient presenting with newly diagnosed LGS or suspected LGS, the recommended first-line treatment continues to be valproate. If this is ineffective as monotherapy, adjunctive therapy with, firstly, lamotrigine and secondly, rufinamide, is recommended. If seizure control remains suboptimal, subsequent adjunctive ASM treatment options include (alphabetically) cannabidiol, clobazam, felbamate, fenfluramine, and topiramate, although evidence for these is more limited. Whenever possible, no more than two ASMs should be used together. Nonpharmacological treatment approaches should be used in conjunction with ASM therapy and include ketogenic diet therapies, vagus nerve stimulation, and corpus callosotomy. Patients with LGS that has evolved from another type of epilepsy who are not already being treated with valproate should be transitioned to valproate and then managed using the same algorithm as for newly diagnosed LGS. Older patients with established LGS should be reviewed at least annually by a suitably experienced neurologist. The revised guidance aims to improve seizure control and quality of life for patients with LGS through personalized,

evidence-based treatment strategies while addressing the challenges of accurate diagnosis and management in a rapidly evolving therapeutic landscape.

Plain Language Summary: Lennox–Gastaut syndrome (LGS) is a severe type of epilepsy that usually starts in childhood but continues into adulthood. It is characterized by a variety of different types of seizures (abnormal electrical activity in the brain), which are difficult to treat and often cause people with the condition to fall and injure themselves. Most people with LGS have learning difficulties and need a lot of support, often in residential care. The authors are experts in treating people with LGS and this article provides up-to-date guidance and advice on how best to care for those with the condition.

KEYWORDS

antiseizure medications, developmental and epileptic encephalopathy, epilepsy, therapy algorithm, update

1 | INTRODUCTION

In 2017, the authors published their guidance on the management of Lennox–Gastaut syndrome (LGS), including details of recommended treatment algorithms and other practical considerations.[1] Since then, there have been important developments in the field, including the publication by the International League Against Epilepsy (ILAE) of updated classification and definitions of developmental and epileptic encephalopathies (DEEs) and other epilepsy syndromes[2,3] and the approval of additional antiseizure medications (ASMs) with novel mechanisms of action (MoAs) for the treatment of seizures associated with LGS.[4–7] As a result of these developments, the authors reconvened to discuss and update their guidance, which is outlined in the current article.

The ILAE uses the term DEE to categorize conditions where the underlying pathology has developmental consequences that are partly independent of those related to the epileptic activity itself.[2,8] LGS is a severe DEE that typically starts between the ages of 18 months and 8 years (most commonly 3–5 years),[3] but it persists through adolescence into adulthood and may also, rarely, have late onset after the age of 18 years.[3,9] Although LGS often occurs in patients without a history of other epileptic syndromes, it may also evolve from other severe infantile seizure disorders, such as infantile epileptic spasms syndrome (IESS), and early infantile DEE.[3,10] Overall, 3.6% of children with epilepsy, and 19% of those whose seizures start in infancy, evolve to LGS,[11] and LGS represents approximately 1%–2% of all epilepsy cases.[3] LGS has a heterogenous etiology and has no biological marker.[1] It may occur due to a brain abnormality (e.g., developmental malformation, tuberous sclerosis, brain insult, infection, and tumor),[12] a genetic pathogenic variant (e.g., *DNM1*, *ALG13*, *CDKL5*, *GABRB1*, *GABRB3*, *SCN1A*, *SCN2A*, and *STXBP1*),[1,13–15] or a metabolic or mitochondrial disease (e.g., Leigh syndrome and creatine metabolic disorders).[16,17] However, etiology is unknown in many cases.[18,19] LGS is associated with a great burden of illness and substantial healthcare costs, due to the need for both home-based and inpatient care.[20,21] Diagnosis is sometimes difficult because the characteristic seizure types and electroencephalogram (EEG) features are not individually pathognomonic when observed by themselves and evolve and change over time.[1] However, early identification of LGS is crucial as it allows for timely intervention. This can potentially improve the clinical trajectory by stabilizing seizure activity, enhancing developmental trajectories, and ultimately improving the overall quality of life (QoL) for patients.[10,22]

2 | DEFINITION OF LGS

In 2022, the ILAE Task Force on Nosology and Definitions published updated classifications and definitions of epilepsy syndromes with onset in childhood, including LGS.[3] The ILAE characterizes LGS by the presence of (i) multiple types of drug-resistant seizures with onset before 18 years (one of which must include tonic seizures), (ii) diffuse, slow spike-and-wave (SSW), and generalized paroxysmal fast activity on EEG, and (iii) cognitive and often behavioral impairments, which may not be present at seizure onset.[3] The full complement of these clinical and EEG features is usually not present at onset, taking time to appear; therefore, young children presenting with characteristic seizure types

but lacking all the aforementioned features should be closely monitored by a specialized medical team for evolution to LGS.[3] Importantly, repetitive assessment for LGS criteria can facilitate access to ASMs approved for LGS.[3] The presence of multiple seizure types (to include tonic seizures and at least one other seizure type) and the EEG features outlined above are mandatory for a definitive diagnosis of LGS.[3]

Tonic seizures occur most often during sleep, typically detected using sleep EEG recording.[3] If tonic seizures occur while the individual is standing, they may lead to falls (drop seizures), often resulting in injury.[3] Additional seizure types associated with LGS include:

- Atypical absence seizures: challenging to identify in individuals with cognitive impairment without a video-EEG recording.[3]
- Atonic seizures: common and frequent, especially in younger patients with LGS.[3] Can cause drop seizures and result in injury.[3]
- Generalized tonic–clonic seizures: may precede the core seizure types of LGS but usually occur later in the disease course.[10]
- Epileptic spasms: in approximately 20% of cases, LGS evolves from IESS[23] and epileptic spasms may persist during the progression to LGS.[24]
- Non-convulsive status epilepticus (NCSE): occurs in 50%–75% of cases, typically consisting of sub-continuous atypical absences, interspersed by recurring brief tonic seizures.[19]
- Focal seizures (with or without bilateral involvement), and unilateral clonic seizures: may precede the core seizure types of LGS but usually occur later in the disease course.[10]
- Myoclonic seizures: occur in approximately 10%–30% of patients and can lead to falls.[18,25–28] However, they are not a defining feature of LGS since they occur in many generalized epilepsies.[22] If myoclonic-atonic seizures are present, the diagnosis of epilepsy with myoclonic atonic seizures (EMAtS) should be considered.[3]

The interictal SSW pattern is characterized by spikes (<70 ms) and sharp waves (70–200 ms), followed by negative high-voltage slow waves (350–400 ms), which occur at a frequency of ≤2.5 Hz and are bilaterally synchronous.[3] Generalized paroxysmal fast activity comprises short bursts of diffuse or bilateral fast activity (≥10 Hz), often occurring during sleep and usually lasting a few seconds or less.[3] The seizure and EEG characteristics outlined above are central features of LGS; however, additional characteristics may be seen. Some or all of these may be present before or at diagnosis, or they may evolve and change over time. In almost all cases, LGS persists into adulthood and seizures remain drug-resistant.[3] Tonic seizures and atypical absence seizures continue to be frequent during adulthood, whereas atonic seizures often decrease in frequency.[3] The SSW pattern decreases in frequency over time and is sometimes absent after the age of 16 years.[3,29,30]

In most cases, developmental impairment is present before seizure onset but the onset of frequent seizures may also result in further developmental stagnation or decline.[3] Over its disease course, LGS culminates in mild to profound intellectual disability in all patients, resulting from developmental slowing, plateauing, or regression over time.[3] Behavioral impairments are common in childhood, adolescence, and adulthood and include hyperactivity with or without attention deficit, autism spectrum disorder, aggression, and sleep disturbances.[3,9]

3 | DIAGNOSTIC CHALLENGES AND CONSIDERATIONS

LGS must be identified and diagnosed as early as possible to ensure that appropriate treatment is received. Searching for the underlying disease may be essential in choosing the most appropriate treatment strategy. Also, the choice of the most appropriate ASMs may avoid the worsening of seizure presentation. In some cases, targeted personalized treatment may be possible (e.g., the presence of *SCN2A* pathogenic variant[31]). Given the challenges associated with accurate LGS diagnosis, several key investigations are recommended, including sleep video-EEG to detect tonic seizures from sleep and paroxysmal fast rhythms[10,29]; magnetic resonance imaging (MRI) with an epilepsy protocol to identify potential structural abnormalities[32]; genetic testing with a gene panel, or preferably whole exome sequencing but also including chromosomal microarray analysis, to detect chromosomal abnormalities and copy number variants[13]; and metabolic testing, if an underlying etiology is not found with imaging or genetic investigation, since LGS can result from a neurometabolic disorder (e.g., Leigh syndrome).[3,16]

None of the seizure types associated with LGS is pathognomonic, so a patient's seizure pattern must be assessed alongside their EEG features if an LGS diagnosis is suspected.[1] The presence of tonic seizures is mandatory for diagnosis and highly suggestive of LGS if seen in the context of a specific EEG pattern. It is also important to bear in mind that the characteristic EEG features of LGS may take time to develop and may not be present initially in patients who transition to LGS from another epilepsy syndrome, such as IESS.[1] However, it is important to try to identify these EEG features at an early stage, since they may also be transient.[30] Indeed, neither the EEG features

nor the seizure types associated with LGS remain static, but develop and change during the disease course, necessitating regular reevaluation and reassessment that might be done at least once in an expert center to ensure appropriate treatment as the syndrome evolves.[1]

Although the use of the aforementioned diagnostic investigations and careful consideration of a patient's clinical and EEG features should allow LGS to be identified, it may be misdiagnosed as other epilepsy syndromes, including, among others, EMAtS (formerly named Doose syndrome), Epileptic Encephalopathy with Spike-and-Wave Activation in Sleep (including Atypical Benign Partial Epilepsy of Childhood[33] [previously called pseudo-Lennox syndrome[34]]), and DEE with Spike Wave Activation in Sleep.[1,3,22] As with early diagnosis, differential diagnosis is crucial to the successful management of LGS. The diagnostic challenges and considerations associated with LGS have been extensively reviewed elsewhere.[1,3,22,35–39]

4 | REVIEW OF CURRENT EVIDENCE FOR TREATMENTS FOR LGS

4.1 | Pharmacological treatment of LGS

Although the evidence base for pharmacological therapy in LGS is limited, ASM treatment options have expanded over recent years to include new agents with novel MoAs (highly purified cannabidiol [CBD] and fenfluramine [FFA]).[40] Despite this, currently available epidemiological evidence indicates a very low likelihood of seizure freedom over the long term.[29,41–43] A Cochrane review of ASMs for LGS, published in 2021, included 11 studies of seven drugs utilized as adjunctive therapy: CBD, cinromide, clobazam (CLB), felbamate (FLB), lamotrigine (LTG), rufinamide (RUF), and topiramate (TPM).[44] The authors concluded that there was high-certainty evidence for overall seizure reduction with adjunctive LTG and RUF, but evidence for other adjunctive ASMs was low to very low.[44] Since then, results of a randomized controlled trial (RCT) of adjunctive FFA in LGS have been published.[45]

4.2 | ASMs licensed or widely used for LGS in Europe and the United States

A summary of ASMs licensed or widely used for LGS in Europe and/or the United States is presented in Table 1.[4,6,45–64] Since the evidence base for sodium valproate (VPA), LTG, RUF, TPM, CLB, and FLB has changed little since previously reviewed by the authors,[1] the remainder of this section will focus on the ASMs that have been approved more recently for treatment of seizures associated with LGS; namely, CBD and FFA.

4.2.1 | Highly purified cannabidiol (CBD)

CBD is licensed by the European Medicines Agency (EMA) as adjunctive therapy, specifically in conjunction with CLB, for seizures associated with LGS in patients aged ≥2 years.[4,65] In the United States, CBD is licensed for the treatment of seizures associated with LGS in patients aged ≥1 year.[5] The efficacy of CBD in treating seizures associated with LGS was demonstrated in two placebo-controlled RCTs[62,63] (Table 1). Patients completing these RCTs could continue into a long-term open-label extension study (median duration, 1090 days; $n = 366$).[66] Reductions in drop seizure and total seizure frequency were maintained over the long term: median percent reductions from baseline ranged from 48% to 71% for drop seizures and from 48% to 68% for total seizures over 156 weeks. Responder rates (≥50% seizure frequency reduction from baseline) ranged from 49% to 68% for drop seizures and from 48% to 65% for total seizures, and seizure freedom rates ranged from 3% to 11% for drop seizures and from 1% to 7% for total seizures. Most AEs were mild or moderate in intensity, and the most common AEs were convulsion (39%), diarrhea (38%), pyrexia (34%), and somnolence (29%).[66] CBD demonstrates many complex interactions with a broad range of hepatic drug-metabolizing enzymes, which may result in significant drug–drug interactions.[40] Clinicians should be aware of such interactions and use CBD wisely, in particular in patients with moderate or severe hepatic impairment. Given the interindividual response and the relationship between the dose administered and CBD blood levels, therapeutic drug monitoring of CBD and concomitant ASMs may be valuable in the clinical management of patients.[67]

In the real-world setting, a Phase 4, retrospective, chart review study assessed the effectiveness and tolerability of adjunctive CBD, without concomitant use of CLB, in 92 patients with LGS and 15 patients with Dravet syndrome aged ≥2 years, who were treated for ≥3 months as part of a European Early Access Program.[68] In patients with LGS, the median change from baseline in drop seizure frequency per 28 days over 3-month intervals varied from −6.2% to −20.9%. A ≥50% reduction in drop seizure frequency was experienced by 18.8% (13/69) of patients after 3 months and 30.2% (16/53) after 12 months, and seizure freedom was achieved by 1.4% (1/69) of patients after 3 months and 3.8% (2/53) after 12 months. The mean number of seizure-free days per 28 days in patients with LGS was 7.0 at baseline and this increased by 1.7 days after 12 months. The most common AEs (≥5% of patients in

TABLE 1 Summary of ASMs licensed or widely used for LGS in Europe and/or the United States.

ASM	MoA	Phase 3 efficacy in drop seizures	Phase 3 efficacy in other seizures associated with LGS	Effect on cognition[a]	Behavioral AEs[a]	Other considerations
VPA	Uncertain. Most likely MoA is potentiation of the inhibitory action of GABA[46]	• No Phase 3 study in LGS	• No Phase 3 study in LGS	• Common[b] AEs: confusional state, hallucinations, disturbance in attention, stupor, memory impairment[46] • Rare[c] AEs: cognitive disorder, learning disorder[46] • An increase in alertness may occur[46]	• Common[b] AEs: aggression, agitation[46] • Rare[c] AE: abnormal behavior[46] • Aggression, hyperactivity, and behavioral deterioration have occasionally been reported[46]	• Should not be used as first-line treatment in female adolescents, in women of childbearing potential, and pregnant women unless alternative treatments are ineffective or not tolerated because of high teratogenic potential and risk of developmental disorders in infants exposed in utero[46]
LTG	Sodium channel blocker[47]; inhibits glutamate release and modulates voltage-gated calcium channels[64]	Phase 3 PBO-controlled RCT in LGS (16-week maintenance period)[48]: • Significantly greater reduction in drop seizures[d] for LTG vs. PBO (−34% vs. −9%; $p = 0.01$) • Significantly higher drop seizure RR[e] for LTG vs. PBO (37% vs. 22%; $p = 0.04$) • Freedom from drop seizures not reported	Phase 3 PBO-controlled RCT in LGS (16-week maintenance period)[48]: • Significantly greater reduction in all seizures for LTG vs. PBO (−32% vs. -9%; $p = 0.002$) • Significantly greater reduction in tonic–clonic seizures for LTG vs. PBO (−36% vs. +10%; $p = 0.03$) • Significantly higher all seizure RR[e] for LTG vs. PBO (33% vs. 16%; $p = 0.01$) • Significantly higher tonic-atonic seizure RR[e] for LTG vs. PBO (43% vs. 20%; $p = 0.007$) • Seizure freedom not reported	Very rare[f] AEs: confusion, hallucinations[47]	Common[b] AEs: aggression, irritability, agitation[47]	• VPA inhibits LTG glucuronidation, reducing its metabolism and increasing its half-life nearly two-fold; therefore, lower LTG doses are required when used concomitantly with VPA[47] • Dose increase required following withdrawal of concomitant VPA therapy
RUF	Modulates activity of sodium channels, prolonging their inactive state[49]	Phase 3 PBO-controlled RCT in LGS (12-week treatment period)[50]: • Significantly greater reduction in drop seizures[g] for RUF vs. PBO (−42.5% vs. +1.4%; $p < 0.0001$) • Significantly higher drop seizure RR[e] for RUF vs. PBO (42.5% vs. 16.7%; $p = 0.002$) • Freedom from drop seizures[g] occurred in 4.1% RUF patients vs. 3.3% PBO patients (p = NS)	Phase 3 PBO-controlled RCT in LGS (12-week treatment period)[50]: • Significantly greater reduction in all seizures for RUF vs. PBO (−32.7% vs. −11.7%; $p = 0.0015$) • Significantly higher all seizure RR[e] for RUF vs. PBO (31.1% vs. 10.9%; $p = 0.0045$) • Significantly greater reduction in absence and atypical absence seizures for RUF vs. PBO (−50.6% vs. −29.8%; $p = 0.0222$) • Significantly greater reduction in atonic seizures for RUF vs. PBO (−44.8% vs. −21.0%; $p = 0.0125$) • No patients were seizure-free during the study • Significantly higher percentage of RUF vs. PBO patients experienced an improvement in seizure severity on parental/guardian GE scale (53.4% vs. 30.6%; $p = 0.0041$)		• Common[b] AE: anxiety[49]	• Common[b] AEs: weight decrease, anorexia, eating disorder, decreased appetite[49]

(Continues)

TABLE 1 (Continued)

ASM	MoA	Phase 3 efficacy in drop seizures	Phase 3 efficacy in other seizures associated with LGS	Effect on cognition[a]	Behavioral AEs[a]	Other considerations
TPM	Potentiates activity of GABA; may modulate $GABA_A$ receptors; inhibits some carbonic anhydrase isoenzymes[51]	Phase 3 PBO-controlled RCT in LGS (11-week double-blind treatment period)[52]: • Significantly greater reduction in drop seizures[g] for TPM vs. PBO (−14.8% vs. +5.1%; $p = 0.041$) • Higher (but not significantly) drop seizure RR[e] for TPM vs. PBO (28% vs. 14%; $p = 0.071$) • During the double-blind phase, 2.2% TPM vs. 0% PBO patients were free from drop seizures[g] • During the maintenance period (last 8 weeks of double-blind phase), 10.9% TPM vs. 0% PBO patients were free from drop seizures[g]	Phase 3 PBO-controlled RCT in LGS (11-week double-blind treatment period)[52]: • Significantly greater reduction in major seizures[g] for TPM vs. PBO (−25.8% vs. +5.2%; $p = 0.015$) • Significantly higher major seizure[h] RR[e] for TPM vs. PBO (33% vs. 8%; $p = 0.002$) • During the double-blind phase, 2.2% TPM vs. 0% PBO patients were free from major seizures[h] • Significantly more TPM vs. PBO patients experienced improvement in seizure severity on the parental GE scale ($p = 0.037$)	• Common[b] AEs: bradyphrenia, expressive language disorder, confusional state, disorientation, disturbance in attention, memory impairment, amnesia, cognitive disorder, mental impairment, psychomotor skills impaired[51] • Many uncommon[i] cognitive AEs[51]	• Very common[j] AE: depression[51] • Common[b] AEs: aggression, mood altered, agitation, mood swings, depressed mood, anger, abnormal behavior[51] • Many uncommon[i] behavioral AEs[51]	• Rare AE: Stevens–Johnson syndrome[51]
CLB	Not fully understood but thought to involve potentiation of GABAergic neurotransmission resulting from binding at the benzodiazepine site of the $GABA_A$ receptor[53]	Phase 3 PBO-controlled RCT in LGS (12-week maintenance period)[54]: • Significantly greater reduction in drop seizures for CLB vs. PBO: average weekly rates decreased 12.1% for PBO vs. 41.2% ($p = 0.0120$), 49.4% ($p = 0.0015$) and 68.3% ($p < 0.0001$) for CLB 0.25, 0.5, and 1 mg/kg/day, respectively • Significantly higher drop seizure RR[e] for CLB vs. PBO: 31.6% for PBO vs. 43.4% (p = NS), 58.6% ($p = 0.0159$), and 77.6% ($p < 0.0001$) for CLB 0.25, 0.5 and 1.0 mg/kg/day, respectively • Rate of freedom from drop seizures was 3.5% for PBO vs. 7.5%, 12.1% and 24.5% for CLB 0.25, 0.5, and 1 mg/kg/day, respectively (statistical comparison not valid due to low patient numbers) • Significantly lower frequency of seizure-related injuries for CLB vs. PBO: 27.1% for PBO vs. 12.1% (p = NS), 4.8% ($p < 0.001$), 10.2% ($p < 0.03$) and 8.9% (≤0.05) for CLB 0.25, 0.5, 1 mg/kg/day and all CLB doses combined, respectively[55]	Phase 3 PBO-controlled RCT in LGS (12-week maintenance period)[54]: • Significantly greater reduction in total seizures for CLB vs. PBO: average weekly rates decreased 9.3% for PBO vs. 34.8% ($p = 0.0414$), 45.3% ($p = 0.0044$) and 65.3% ($p < 0.0001$) for CLB 0.25, 0.5, and 1 mg/kg/day, respectively	• Common[b] AEs: disturbance in attention, slow speech/dysarthria / speech disorder[56] • Uncommon[k] AEs: amnesia (may be associated with abnormal behavior), memory impairment, anterograde amnesia (especially at higher dose levels), confusional state[56]	• Common[b] AEs: irritability, aggression, restlessness, depression[56] • Uncommon[k] AEs: abnormal behavior, anxiety, delusion, nightmare[56] • Amnesia effects may be associated with inappropriate behavior[56]	• Tolerance and physical and/or psychic dependence may develop, especially during prolonged use[56]: in a long-term, single-center LGS study, tolerance developed in 48% of initial responders[57] • Discontinuation may result in withdrawal or rebound phenomena[56] • May change VPA plasma levels when used concomitantly; plasma levels of VPA should therefore be monitored[56] • May decrease LTG plasma levels (expert opinion) • Concomitant use of CLB and CBD increases the incidence of somnolence and sedation[56,58]

TABLE 1 (Continued)

ASM	MoA	Phase 3 efficacy in drop seizures	Phase 3 efficacy in other seizures associated with LGS	Effect on cognition[a]	Behavioral AEs[a]	Other considerations
FLB	Unclear.[59] Acts as non-competitive GluN2B antagonist; inhibits Na^+/Ca^{2+} channels with potentiation of GABA-induced chloride currents, leading to inhibition of NMDA receptors[60]	PBO-controlled RCT in LGS (70-day treatment period; 56-day maintenance period)[61]: • During the treatment period, significantly greater reduction in atonic seizures for FLB vs. PBO (−34% vs. −9%; $p=0.01$); 3/28 FLB-treated patients vs. 0/22 PBO-treated patients had no atonic seizures • During the maintenance period, significantly greater reduction in atonic seizures for FLB vs. PBO (−44% vs. −7%; $p=0.002$); 5/28 FLB-treated patients vs. 0/22 PBO-treated patients had no atonic seizures	PBO-controlled RCT in LGS (70-day treatment period; 56-day maintenance period)[61]: • During the treatment period, significantly greater reduction in parental counts of all seizures for FLB vs. PBO (−19% vs. +4%; $p=0.002$); no patients were seizure-free • During the maintenance period, significantly greater reduction in parental counts of all seizures for FLB vs. PBO (−26% vs. +5%; $p<0.001$); 4/37 FLB-treated patients vs. 1/36 PBO-treated patients had no seizures • During treatment period, reduction in generalized tonic–clonic seizures was −28% for FLB vs. +11% for PBO ($p=$ NS); 2/16 FLB-treated patients vs. 1/13 PBO-treated patients had no generalized tonic–clonic seizures • During the maintenance period, significantly greater reduction in generalized tonic–clonic seizures for FLB vs. PBO (−40% vs. +12%; $p=0.017$); 7/16 FLB-treated patients vs. 1/13 PBO-treated patients had no generalized tonic–clonic seizures • During the maintenance period, significantly higher parent/guardian GE scores for FLB vs. PBO from day 49 onward ($p<0.001$)	In controlled pediatric LGS studies, 6.5% of patients reported abnormal thinking[59]	• Frequent AEs: agitation, psychological disturbance, aggressive reaction[59] • Infrequent AEs: hallucination, euphoria, suicide attempt[59] • In controlled pediatric LGS studies, 16.1% of patients reported nervousness and 6.5% of patients reported emotional lability[59]	• Black box warning over risk of aplastic anemia and acute liver failure[59] • Only available for limited use in Europe on a patient-by-patient basis, due to the risk of aplastic anemia and liver failure
CBD	Unclear but does not exert its anticonvulsant effect through interaction with cannabinoid receptors.[4] Reduces neuronal hyper-excitability through modulation of intracellular calcium via GPR55 and TRPV-1 channels; modulates adenosine-mediated signaling through inhibition of adenosine cellular uptake via ENT-1[4]	Two Phase 3 PBO-controlled RCTs in LGS (GWPCARE3 and GWPCARE4; 14-week treatment periods)[62,63]: GWPCARE3[62]: • Significantly greater reduction in drop seizure[l] frequency for CBD vs. PBO: median frequency decreased 17.2% for PBO vs. 37.2% ($p=0.002$) and 41.9% ($p=0.005$) for CBD 10 and 20 mg/kg/day, respectively • Significantly higher drop seizure[l] RR[e] for CBD vs. PBO: 14% for PBO vs. 36% ($p=0.003$) and 39% ($p<0.001$) for CBD 10 and 20 mg/kg/day, respectively • Higher drop seizure[l] freedom rate during maintenance phase (12 weeks) for CBD vs. PBO: 1% for PBO vs. 4% and 7% for CBD 10 and 20 mg/kg/day, respectively (statistical comparison not performed); no patient was free of drop seizures during the entire 14-week treatment period GWPCARE4[63]: • Significantly greater reduction in drop seizure[l] frequency for CBD vs. PBO: median frequency decreased 21.8% for PBO vs. 43.9% for CBD 20 mg/kg/day ($p=0.0135$) • Significantly higher drop seizure[l] RR[e] for CBD vs. PBO: 24% for PBO vs. 44% for CBD 20 mg/kg/day ($p=0.0043$) • Significantly higher drop seizure[l] freedom rate during maintenance phase (12 weeks) for CBD vs. PBO: 0% for PBO vs. 6% for CBD 20 mg/kg/day ($p=0.0246$); no patient was free of drop seizures during the entire 14-week treatment period	Two Phase 3 PBO-controlled RCTs in LGS (GWPCARE3 and GWPCARE4; 14-week treatment periods)[62,63]: GWPCARE3[62]: • Significantly greater reduction in total seizure frequency for CBD vs. PBO: median frequency decreased 18.5% for PBO vs. 36.4% ($p=0.002$) and 38.4% ($p=0.009$) for CBD 10 and 20 mg/kg/day, respectively • Greater reduction in non-drop seizure frequency for CBD vs. PBO: median frequency decreased 34.3% for PBO vs. 61.1% and 54.6% for CBD 10 and 20 mg/kg/day, respectively (statistical comparison not performed) GWPCARE4[63]: • Significantly greater reduction in total seizure frequency for CBD vs. PBO: median frequency decreased 13.7% for PBO vs. 41.2% for CBD 20 mg/kg/day ($p=0.0005$) • Significantly greater reduction in non-drop seizure frequency for CBD vs. PBO: median frequency decreased 22.9% for PBO vs. 49.4% for CBD 20 mg/kg/day ($p=0.0044$)	• Common[b] AE: lethargy[4]	• Common[b] AEs: irritability, aggression[4]	• Very common[j] AEs include somnolence, decreased appetite[4] • CBD can cause dose-related elevations of liver transaminases, particularly in patients taking concomitant VPA[4] • Concomitant use of CLB and CBD increases the incidence of somnolence and sedation[58]

(Continues)

TABLE 1 (Continued)

ASM	MoA	Phase 3 efficacy in drop seizures	Phase 3 efficacy in other seizures associated with LGS	Effect on cognition[a]	Behavioral AEs[a]	Other considerations
FFA	Serotonin-releasing agent that stimulates multiple 5-HT receptor sub-types through the release of serotonin; may reduce seizures by acting as an agonist at specific serotonin receptors, including the 5-HT1D, 5-HT2A, and 5-HT2C receptors, and also by acting on the sigma-1 receptor[6]	Phase 3 PBO-controlled RCT in LGS[45]: • Significantly greater reduction in drop seizure[m] frequency for FFA vs. PBO: median frequency decreased 7.6% for PBO vs. 14.2% (p = NS) and 26.5% (p = 0.001) for FFA 0.2 and 0.7 mg/kg/day, respectively • Significantly higher drop seizure[m] RR[e] for FFA vs. PBO: 10% for PBO vs. 28% (p = 0.005) and 25% (p = 0.02) for FFA 0.2 and 0.7 mg/kg/day, respectively • GTCS were more responsive to FFA than other seizure types	Phase 3 PBO-controlled RCT in LGS[45]: • Significantly greater reduction in the frequency of all countable motor seizures[n] for FFA vs. PBO: median frequency decreased 8.4% for PBO vs. 11.8% (p = NS) and 26.3% (p = 0.003) for FFA 0.2 and 0.7 mg/kg/day, respectively • Significantly greater proportion of patients rated as "very much improved" or "much improved" by site investigators on CGI-I for FFA vs. PBO: 6% for PBO vs. 20% (p = 0.01) and 26% (p = 0.001) for FFA 0.2 and 0.7 mg/kg/day, respectively • Significantly greater proportion of patients rated as "very much improved" or "much improved" by caregivers on CGI-I for FFA vs. PBO: 5% for PBO vs. 27% (p < 0.001) and 34% (p < 0.001) for FFA 0.2 and 0.7 mg/kg/day, respectively	• Common[b] AE: lethargy[6]	• Common[b] AE: aggression[6]	• Very common[j] AEs include decreased appetite[6]

Abbreviations: AE, adverse event; ASM, antiseizure medication; Ca^{2+}, calcium ion; CBD, cannabidiol; CGI-I, Clinical Global Impression-Improvement scale; CLB, clobazam; ENT-1, equilibrative nucleoside transporter 1; FFA, fenfluramine; FLB, felbamate; GABA, gamma aminobutyric acid; GE, global evaluation; GPR55, G protein-coupled receptor 55; GTCS, generalized tonic–clonic seizures; LGS, Lennox–Gastaut syndrome; LTG, lamotrigine; Na^{+}, sodium ion; NMDA, *N*-methyl-D-aspartate receptor; NS, not significant; PBO, placebo; RCT, randomized controlled trial; RR, responder rate; RUF, rufinamide; TPM, topiramate; TRPV-1, transient receptor potential vanilloid 1; VPA, valproate.

[a]Effects on cognition and behavioral AEs are based on each ASM's European Union Summary of Product Characteristics, with the exception of FLB, for which the United States Prescribing Information was used (since not approved in the European Union);

[b]≥1/100 to <1/10;

[c]≥1/10000 to <1/1000;

[d]Tonic, atonic, and major myoclonic seizures;

[e]≥50% seizure frequency reduction from baseline;

[f]<1/10000;

[g]Tonic-atonic seizures;

[h]Drop seizures and tonic–clonic seizures;

[i]≥1/1000 to <1/100;

[j]≥1/10;

[k]≥1/1000 to <1/100;

[l]Atonic, tonic and tonic–clonic seizures;

[m]Generalized tonic–clonic, focal to bilateral tonic–clonic, tonic, atonic, or tonic or atonic seizures;

[n]Generalised tonic–clonic, tonic, clonic, atonic, tonic or atonic, and clearly recognizable focal seizures.

the overall LGS and Dravet population) were somnolence (5.6%) and diarrhea (5.6%).[68] Similar results emerged from a large Italian Expanded Access Program study, in which CBD was administered to 93 individuals with highly refractory LGS ($n=63$) or Dravet syndrome ($n=30$) for 12 months.[69] After 12 months, the responder rate (≥50% seizure frequency reduction from baseline) and seizure freedom rate were 49.0% and 3.9%, respectively, for total seizures, and 45.1% and 7.8%, respectively, for convulsive seizures (i.e., clonic, tonic, tonic–clonic, atonic, and focal to the bilateral tonic–clonic). The most frequently reported AEs (≥10% of patients) were somnolence (22.6%), diarrhea (11.8%), and transaminase elevation (10.7%).[69]

4.2.2 | Fenfluramine (FFA)

FFA is licensed in Europe as adjunctive therapy for seizures associated with LGS in patients aged ≥2 years,[6] and in the United States for the treatment of seizures associated with LGS in patients aged ≥2 years.[7] The efficacy of FFA in treating seizures associated with LGS was established in a Phase 3 placebo-controlled RCT[45] (Table 1). Patients completing this RCT could continue into a long-term open-label extension study (currently ongoing; median duration, 364 days; $n=247$ [October 2020]).[70] An interim analysis of the open-label extension study demonstrated that efficacy was maintained over the long term: the median reduction in monthly drop seizure frequency was 28.6% over the entire open-label extension ($p<0.0001$) and 50.5% at Month 15 ($p<0.0001$); 31.1% of patients experienced ≥50% reduction in drop seizure frequency over the entire open-label extension and 51.2% after approximately 1 year.[70] The longest interval between drop seizures increased from a median of 2.0–7.0 days.[70,71] Generalized tonic–clonic seizures and tonic seizures were most responsive to treatment, with median reductions over the entire open-label extension of 48.8% and 35.8%, respectively ($p<0.0001$ for both).[70] The median reduction in non-drop seizure frequency was 45.9% ($p=0.0038$). Approximately one-third of investigators (37.6%) and caregivers (35.2%) rated their patients as having "very much improved" or "much improved" on the Clinical Global Impression of Improvement at the last assessment. The most frequent treatment-emergent AEs were decreased appetite (16.2%) and fatigue (13.4%).[70] There were no cases of valvular heart disease or pulmonary arterial hypertension in either the initial Phase 3 RCT or open-label extension study,[45,70] despite FFA being originally withdrawn from the market for this reason when previously developed as an appetite suppressant for the treatment of obesity.[40] The EMA states that echocardiogram monitoring should be conducted every 6 months for the first 2 years of FFA treatment and annually thereafter,[6] and the US Food and Drug Administration states that echocardiogram assessments should be obtained before, during (every 6 months), and once after (3–6 months) the final dose of FFA.[7]

In the real-world setting, a Spanish, single-center, retrospective, post-marketing study assessed the effectiveness and tolerability of FFA when used in routine clinical practice to treat patients with Dravet syndrome or other developmental and genetic epileptic encephalopathies ($n=54$) and LGS ($n=14$).[72] Seizure frequency data were available for 13 patients with LGS. After 12 months, the sustained responder rate (≥50% seizure frequency reduction from baseline for ≥2 consecutive months) and seizure freedom rate in the patients with LGS were 50.0% and 8.3%, respectively. In the overall study population (i.e., patients with Dravet syndrome and LGS), the most frequently reported AEs (≥10% of patients) were decreased appetite (35.9%), somnolence (15.9%), and irritability (15.6%). No cases of pulmonary arterial hypertension or valvular heart disease were observed.[72]

4.3 | Use of ASMs not approved for drop seizures in LGS

Soticlestat is a first-in-class selective inhibitor of cholesterol 24-hydroxylase (CH24H) that is being investigated as an adjunctive ASM for DEEs, including LGS.[40,73,74] A Phase 2 placebo-controlled RCT assessed the efficacy and safety of soticlestat in patients aged 2–17 years with LGS ($n=88$) and Dravet syndrome ($n=51$).[74] During the 12-week maintenance period, the median placebo-adjusted percent reduction in the frequency of drop seizures in patients with LGS was 17.1% ($p=$ not significant). In the combined population, the most frequently reported treatment-emergent AEs (≥5% greater with soticlestat vs. placebo) were lethargy and constipation.[74] Phase 3 trials of soticlestat in patients with LGS are currently ongoing (ClinicalTrials.gov NCT04938427 and NCT05163314); however, it was recently announced that one of these (NCT04938427) failed to meet its primary endpoint (reduction in major motor drop seizures).[75] A Phase 3 placebo-controlled trial of carisbamate (which belongs to the alkyl-carbamate family of drugs that also includes FLB[40]) in adult and pediatric patients with LGS is also currently ongoing (ClinicalTrials.gov NCT05219617).

A recent systematic review and meta-analysis offers a comprehensive assessment of steroid efficacy beyond IESS.[76] However, the level of evidence for LGS is low[76] and clinicians should be cautious in extrapolating these findings directly to LGS due to the distinct pathophysiological mechanisms involved. There remains a notable gap between the absence of RCTs evaluating the efficacy of

steroids in treating LGS and their widespread utilization in many medical centers. Although no RCTs have been conducted to date,[10] anecdotal evidence suggests that steroids may offer short-term benefits in managing atypical absence seizures, drop seizures, and NCSE.[1] However, it is important to acknowledge that relapse is frequent.[1] Furthermore, prolonged usage of steroids carries the risk of serious adverse effects, such as hyperlipidemia, osteoporosis, and growth suppression.[77] Consequently, it is advisable to reserve steroid administration for acute worsening periods, steering clear of prolonged usage, according to current recommendations.[1]

4.4 | Real-world evidence for the use of pharmacological agents in the treatment of LGS

Several ASMs (both approved and not approved for use in LGS) have been specifically assessed in patients with LGS in the real-world clinical practice setting.

4.4.1 | Real-world evidence for ASMs approved for use in LGS

The greatest amount of real-world evidence is for RUF (approximately 15 studies worldwide), and this has been reviewed elsewhere.[78–80] In summary, clinical practice studies of RUF have confirmed evidence from clinical trials, demonstrating that it is effective and generally well tolerated in children as young as 1 year and adults, and that it may be particularly effective in treating drop seizures and generalized tonic–clonic seizures.[79] They also indicate that a "low and slow" approach to RUF dosing and titration can improve tolerability while maintaining effectiveness.[78]

4.4.2 | Real-world evidence for ASMs not approved for use in LGS

Some broad-spectrum ASMs may be useful in treating seizures associated with LGS, despite having limited evidence of use specifically in patients with LGS. These include levetiracetam (LEV), zonisamide (ZNS), and perampanel (PER). A Phase 3 trial of adjunctive PER in patients with LGS was terminated early due to recruitment challenges, exacerbated by the COVID-19 pandemic,[81] and all other evidence for these three ASMs comes from the clinical practice setting. A multicenter, open-label, observational study conducted in 55 patients with LGS assessed the efficacy and tolerability of adjunctive LEV over an 8-week maintenance period.[82] A >50% seizure frequency reduction was observed in 32 (58.2%) patients and 15 (27.3%) achieved seizure freedom; seven of 12 (58.3%) patients with drop seizures experienced a >50% seizure frequency reduction. The most frequently reported AE was hyperactivity (12.7%).[82] A multicenter study conducted in Korea in 62 patients with LGS assessed the efficacy and safety of adjunctive ZNS over ≥12 months.[83] A >50% seizure frequency reduction was observed in 32 (51.6%) patients, three of whom achieved seizure freedom. AEs included transient somnolence and anorexia.[83] In a prospective study of 13 patients with LGS who were treated with adjunctive PER over a mean follow-up duration of 10.8 months, nine (69.2%) were responders (≥50% reduction in total seizure frequency), and nine (69.2%) were rated by their clinician as "much improved" or "very much improved."[84] Four patients (30.8%) discontinued PER due to the lack of efficacy ($n = 2$) and seizure aggravation ($n = 2$), and six patients (46.2%) experienced AEs (decreased activity/social interaction, $n = 3$; behavioral disturbance with agitation, $n = 2$; fatigue, $n = 2$). Seven patients (53.8%) experienced improvements in cognitive function and/or behavior.[84] A multicenter, retrospective, observational cohort study assessed the long-term effectiveness of adjunctive PER in 87 patients with LGS.[85] During a median follow-up of 11 months, responder rates (≥50% seizure frequency reduction from baseline) were 41.4% for all seizure types and 61.1% for drop seizures. Seizure relapse occurred in 36.1% of patients over 36 months, but none of the patients experienced seizure worsening during PER treatment. The most common AEs (≥10% of patients) were behavioral disturbances (21.8%) and somnolence (12.6%).[85] Another retrospective, open-label study assessed the efficacy and tolerability of adjunctive PER when used to treat 71 adult patients with LGS (mean age, 40.1 years; 62 with "pure LGS"; nine with "LGS-like epileptic encephalopathy") over a median duration of 539 days.[86] The overall responder rate (≥50% seizure frequency reduction) was 64.8%, with 16.9% of patients experiencing ≥90% seizure frequency reduction. Six patients (8.5%) experienced seizure aggravation with PER. Negative behavioral changes were observed in 32.4% of patients, but "positive side effects" (feelings of wellness and calm; improved contact) were observed in 5.6% of patients.[86] Finally, a retrospective study assessed the 12-month effectiveness and tolerability of adjunctive cenobamate in four adults with LGS (aged 27–37 years).[87] At 12 months, the seizure frequency reduction from baseline ranged from 25% to 74%, with two patients experiencing ≥50% seizure frequency reduction. AEs included somnolence ($n = 2$) and ataxia, dizziness, and vomiting ($n = 1$).[87]

4.5 | Non-pharmacological treatment of LGS

Non-pharmacological treatment options for LGS include ketogenic diet therapies (KDT), resective surgery, vagus nerve stimulation, corpus callosotomy, and deep brain stimulation. Since the evidence base for the use of all of these treatments, except deep brain stimulation, has changed little since previously reviewed by the authors,[1] these are summarized in Table 2.[1,88–114]

TABLE 2 Summary of non-pharmacological treatment options for LGS.

Treatment	Key details

Ketogenic diet therapies (Ketogenic diet; Modified Atkins diet)	• Substantial evidence of efficacy and safety/tolerability in LGS:
	  • A 2012 literature review of 18 studies found that 47% of patients experienced >50% seizure frequency reduction and 16% achieved seizure freedom after 3–36 months[88]
	  • A 2022 literature review of seven studies found that 17%–73% of patients experienced ≥50% seizure frequency reduction and 1%–24% of patients achieved seizure freedom after treatment durations of 1 month to 19 years[89]
	• Minimal AEs, generally alleviated by adjusting diet[1]
	• Response is usually observed within 3 months, allowing effectiveness to be assessed relatively quickly[1]
	• Requires a dedicated ketogenic diet team and commitment from carers[1]

Resective surgery	• All patients should be investigated for a potential localized brain abnormality (although not frequently found) since resective surgery can be curative in carefully selected individuals[1]
	• In a retrospective review of 90 patients with LGS who underwent resective surgery, the most common pathological finding was malformation of cortical development[90]
	  • During a mean postoperative follow-up duration of 6.1 years, 45 patients (50.0%) were seizure-free and 15 (16.7%) reported infrequent seizures[90]
	  • Seizure-free patients demonstrated significantly better adaptive behavior and social competence versus patients with persistent seizures ($p < 0.05$)[90]

Vagus nerve stimulation	• Some evidence of effectiveness in LGS[91–95] • A meta-analysis of seven prospective and 10 retrospective studies in patients with LGS ($N = 480$) demonstrated a responder rate of 54%[96] • Recommended in AAN guidelines as a treatment option for LGS (Level C)[91] • AEs are typically stimulation-related, reversible, mild to moderate in intensity, and usually decrease over time; AEs seldom require device removal[97] • Patient may experience continuing improvement over time, and improvement in alertness[98] • Can be used with other pharmacological and non-pharmacological therapies; does not interact with ASMs[1] • Less invasive than callosotomy, but involves implantation of a device[1] • Re-evaluation of patients for the presence of a seizure focus may be appropriate following vagus nerve stimulation, as generalized epileptiform discharges may become more localized[1,99]
Corpus callosotomy	• Some evidence of effectiveness in LGS[100–104] • Particularly effective for atonic seizures/drop seizures (more effective than vagus nerve stimulation)[100,105] • Recommended for use when drop seizures are especially problematic[1] • Other treatments can be used following corpus callosotomy if needed[1] • Less invasive techniques, such as radiosurgical corpus callosotomy or stereotactic laser anterior corpus callosotomy, have obtained similar results in terms of efficacy in controlling drop seizures[106,107] • A complete corpus callosotomy could be more efficacious than an anterior corpus callosotomy for some seizure types[105] • Following complete corpus callosotomy, transient disconnection syndrome has been observed in 50% of patients but this resolved in all the patients following 2 years of follow-up[108] • Re-evaluation of patients for the presence of a seizure focus may be appropriate following corpus callosotomy, as generalized epileptiform discharges may become more localized[1,99]
Deep brain stimulation	• Several studies have reported favorable outcomes in patients with LGS when the centromedian thalamic nucleus has been targeted with deep brain stimulation, with seizure reductions of 25–100% reported[109–113] • Cognitive effects and side effects of deep brain stimulation of the centromedian thalamic nucleus are currently unclear[114] • Mood and memory problems have been reported following DBS of the anterior thalamic nucleus, but it is conceivable that different thalamic structures might vary in their role in cognition and mood[114] • More research is required to establish the potential utility of deep brain stimulation in LGS[114] • More expensive than other non-pharmacological treatment options, such as vagus nerve stimulation[114]

Abbreviations: AAN, American Academy of Neurology; AE, adverse event; ASM, antiseizure medication; LGS, Lennox–Gastaut syndrome.

DBS is an emerging treatment for drug-resistant epilepsies, including LGS. Given the heterogeneous nature of LGS, certain etiologies may be more responsive to DBS than others. A better understanding of anatomical targets, stimulation parameters, neurophysiological biomarkers, and appropriate patient selection would help clarify the potential utility of DBS in LGS.[114]

5 | GENERAL PRINCIPLES OF LGS TREATMENT

LGS is a DEE with a very poor prognosis in terms of long-term seizure control and cognitive function. Despite a range of treatment options, the achievement of seizure freedom is very unlikely.[115] LGS adversely affects the QoL of both patients and caregivers[20,116–118]; seizure control (particularly drop seizure control) and days without seizures being the main determinants of QoL in LGS.[119,120] From childhood to adulthood, management of LGS must carefully balance the burden of treatment against its potential side effects, always focusing on the patient's overall QoL[9]; consequently, the goal of treatment should be optimal seizure control (particularly with regards to the more disabling seizure types), rather than seizure freedom.[1] Treatment goals may change according to the patient's age and stage of disease, and this should be addressed as a key part of ongoing re-evaluation and transition of care.[1] Treatment goals and plans should be reassessed regularly by centers of reference with extensive experience in the treatment of rare and complex epilepsies, and plans should include a transparent explanation of potential AEs and how these should be managed.[1,10]

In the context of LGS, a personalized approach to treatment can be complex, due to the nature of the syndrome itself. LGS is characterized by a variety of different seizure types and a spectrum of cognitive impairments, along with a diverse range of etiologies that can contribute to its development. This heterogeneity makes it challenging to tailor treatments to individual patient profiles since what may be effective for one person may not be for another. Additionally, the syndrome often requires a multifaceted treatment strategy that includes a combination of medications, dietary treatment, and potentially surgical interventions. Due to the complexity of LGS, treatment strategies must be highly individualized and frequently adjusted to accommodate the unique and evolving needs of each patient. This tailored approach is essential for managing the multiple seizure types and comorbidities commonly associated with LGS, ultimately aiming to optimize therapeutic outcomes in this challenging patient population.

It is important to note, however, that while a personalized approach may be difficult, it is not entirely unfeasible. It requires careful consideration of each patient's unique circumstances, including the etiology of their condition, the specific characteristics of their seizures, their response to previous treatments, and their overall health status. A thorough evaluation by a team of specialists can help in creating a more tailored treatment plan, but it does require ongoing assessment and adjustments, which can be resource-intensive. Moreover, there is preliminary evidence that computational methods for assessing multiple phenotypic features in specific epileptic disorders might help facilitate the development of future precision-medicine approaches.[121]

6 | TREATMENT ALGORITHMS FOR LGS

The following recommendations and practical advice are the authors' expert opinions, based on the available evidence and their clinical experience, and include relevant updates to the 2017 guidance.

The clinical features diagnostic of LGS may evolve with time, and this must consequently remain a consideration when planning therapy in young children presenting with multiple seizure types. Since it may take time for patients to develop all the clinical and EEG features of LGS, it is recommended that—once all attempts to exclude other diagnoses have been undertaken—a patient presenting with features suggestive of LGS should be treated as though they have LGS until their full clinical/EEG profile becomes clear.

6.1 | Newly diagnosed patients with LGS and patients with LGS already receiving ASM therapy

The treatment algorithm for a newly diagnosed patient with LGS or a patient with LGS already receiving ASM therapy is presented in Figure 1.[36]

6.1.1 | Patients with newly diagnosed LGS or suspected LGS

For a patient presenting with newly diagnosed LGS or suspected LGS, the recommended first-line treatment is VPA (Figure 1). VPA should generally not be used in women of childbearing potential, due to its high teratogenic potential,[46] unless no suitable alternatives exist, and effective contraception is used. It is important to consider that female patients with LGS are generally unlikely to have children due to the severity of their condition. The

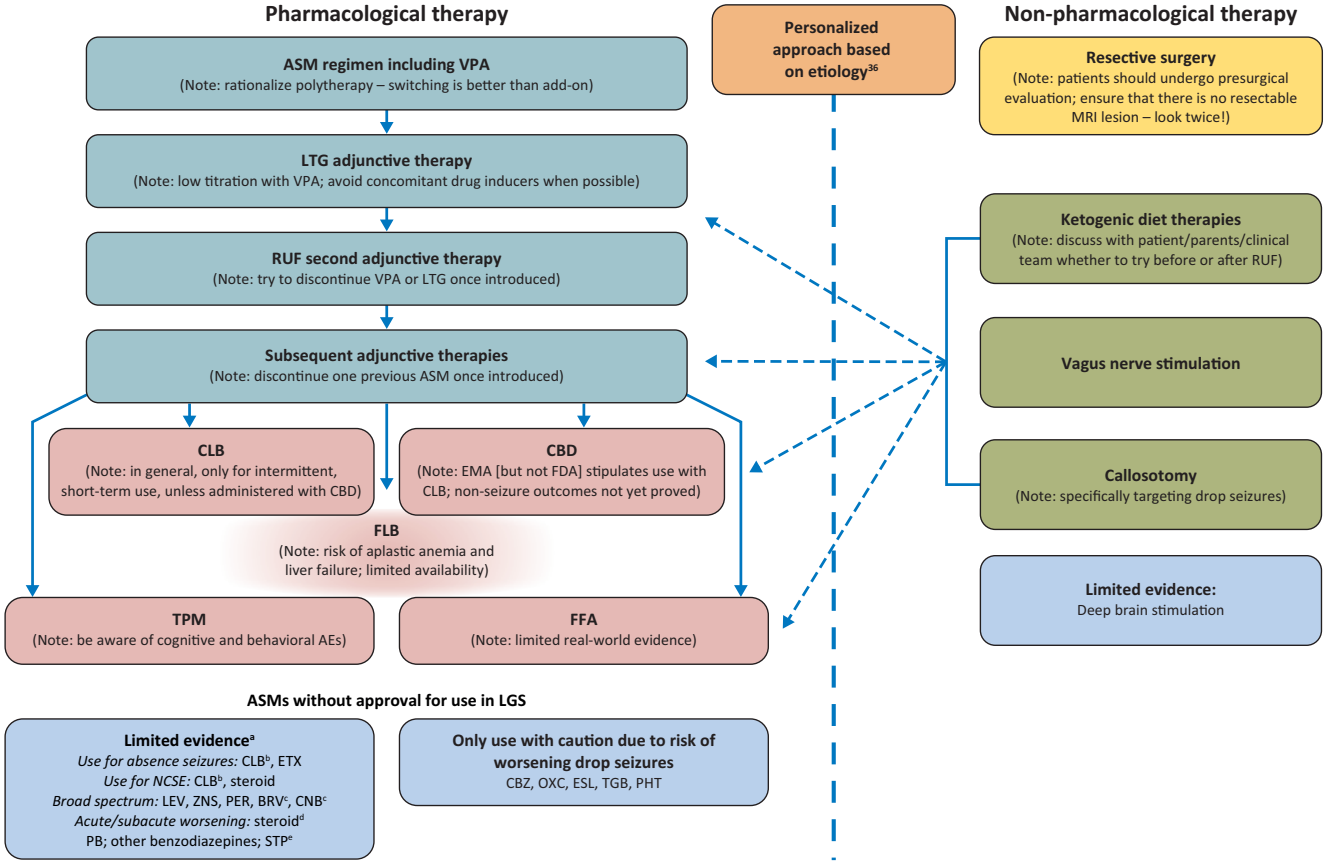

FIGURE 1 Treatment algorithm for a newly diagnosed patient with LGS or a patient with LGS already receiving ASM therapy. [a]Could be considered according to the most prevalent seizure type; [b]CLB is used without validation from an RCT or other high-level evidence study; [c]BRV and CNB are broad-spectrum ASMs without any specific evidence in LGS; [d]With clinical goals; [e]In combination with VPA and/or CLB. AE, adverse event; ASM, antiseizure medication; BRV, brivaracetam; CBD, cannabidiol; CBZ, carbamazepine; CLB, clobazam; CNB, cenobamate; EMA, European Medicines Agency; ESL, eslicarbazepine acetate; ETX, ethosuximide; FDA, Food and Drug Administration; FFA, fenfluramine; FLB, felbamate; LEV, levetiracetam; LGS, Lennox–Gastaut syndrome; LTG, lamotrigine; MRI, magnetic resonance imaging; NCSE, non-convulsive status epilepticus; OXC, oxcarbazepine; PB, phenobarbital; PER, perampanel; PHT, phenytoin; RCT, randomized controlled trial; RUF, rufinamide; STP, stiripentol; TGB, tiagabine; TPM, topiramate; VPA, sodium valproate; ZNS, zonisamide.

risk–benefit ratio must be carefully balanced in each case. If VPA therapy does not provide adequate seizure control, LTG should be added as the first adjunctive therapy. Since VPA inhibits LTG metabolism, a decreased LTG dose with slow titration should be used. If VPA plus LTG does not provide adequate seizure control, RUF should be initiated as adjunctive therapy. Once RUF has been initiated, attempts should be made to discontinue either VPA or LTG, and, if VPA is discontinued, the LTG dose should be increased. When considering adding an adjunctive therapy, every attempt should be made to discontinue one of the two previous ASMs once the new ASM has been introduced, since there is no evidence for the effectiveness of more than two ASMs in combination, and the use of multiple ASMs unnecessarily raises the risk of side effects and/or drug–drug interactions.

If adequate seizure control is not achieved with the addition of RUF, the choice of the next adjunctive ASM should be discussed with the patient/parent/caregiver/clinical team, based on the patient's clinical profile and taking the caregiver's experience into consideration. When discussing further ASM options, the following points should be considered:

- Short-term treatment with CLB may be considered, temporarily increasing the ASM load. Since there might be a risk of tolerance, dependence, and cognitive/behavioral AEs, CLB should preferably be used on an intermittent, short-term (3–5 days) basis when acute episodes occur (expert opinion). Such episodes include sustained absence seizures (duration >1 day), cluster seizures, and NCSE. This aside, where tolerance is not an issue, CLB may prove a useful adjunctive ASM, particularly where drop seizures are troublesome. It should be noted that high-dose benzodiazepines may increase sleepiness and consequently increase the risk of tonic seizures.

- There is increasing evidence supporting the use of CBD as adjunctive therapy in LGS patients,[122] although this requires confirmation in further trials and long-term safety studies.
- Although considered a useful treatment option in LGS, particularly for drop seizures,[123] FLB is not licensed by the EMA due to associated risks of aplastic anemia and liver failure. However, in some countries (e.g., France, Italy, Spain, and United Kingdom) it is authorized for use when prescribed by hospital-based expert teams, and its use is therefore likely to be country-specific. FLB could be considered as an early adjunctive treatment option in LGS, with careful consideration of its potential benefits against its risks.[124] If deemed necessary, it is advisable to closely monitor the patient, including regular blood counts and liver function tests.
- TPM is licensed for LGS and may be used once other lines of treatment have been tried, but it has a greater potential for cognitive and behavioral adverse effects than other marketed ASMs.
- FFA has been a relatively recent addition to the options approved for the treatment of seizures associated with LGS. It may have particular efficacy in treating generalized tonic–clonic seizures. Real-world evidence for the use of FFA in LGS is currently limited.
- ASMs used to treat LGS may be associated with behavioral and cognitive AEs,[125] which should be considered when selecting an ASM at the individual patient level.

Based on the authors' clinical experience, several ASMs that do not have a specific license for LGS may nevertheless be considered as adjunctive therapy options. Given the variety of seizure types that may be present in the same patient, consideration should be given to the evidence for a particular ASM in the treatment of the specific seizure type(s) present (rather than the syndrome per se), with the caveat that the treating clinician is knowledgeable and up-to-date on the potential risks for drug–drug interactions. LEV, ZNS, and PER have demonstrated some evidence of effectiveness in LGS. All are broad-spectrum in their modes of action and may therefore be useful in treating multiple seizure types. LEV particularly may be a useful adjunct as it has few interactions with other medications. Ethosuximide can be useful for the treatment of absence seizures but should always be combined with an ASM that is effective in treating generalized tonic–clonic seizures and tonic/atonic seizures since it is not effective for these seizure types. CLB may also be useful for the treatment of absence seizures. Benzodiazepines other than CLB may be considered for intermittent, short-term use for acute episodes (as recommended for CLB), but should not be used in combination with each other. Although there is no published evidence to support the efficacy of stiripentol (STP) in treating LGS, it can be used in combination with VPA and/or CLB. The usual approach is to add STP to VPA and subsequently add a small dose of CLB if required. It should be noted that STP will increase VPA and CLB levels, so some dose adjustments might be required. Carbamazepine, oxcarbazepine, eslicarbazepine acetate, tiagabine, and phenytoin should only be used with caution, due to the potential risk of aggravation of drop seizures with a myoclonic component (expert opinion).

The use of non-pharmacological treatment approaches should be considered alongside the use of ASMs and discussed from the outset as part of the patient's treatment plan. Some patients/parents/caregivers may propose trying KDT relatively early on in the patient's treatment pathway. If this is the case, KDT can be tried if VPA plus LTG does not provide an adequate seizure response, before RUF is initiated. Alternatively, KDT may be introduced later, when multiple ASMs have been tried. Since response to KDT is usually observed within 3 months,[126] this therapeutic option can be explored relatively quickly.

An evaluation regarding resective surgery or disconnective surgery must be considered in all patients, particularly those with LGS with structural etiology who have lesions predominantly in one hemisphere or tuberous sclerosis. This should be conducted by a specialized team with extensive experience in pre-surgical evaluation. As callosotomy involves surgery (except when a gamma knife is used, which is not widely available), its use will largely depend on patient/parent/caregiver choice, considering it is targeted at drop seizures. Complete callosotomy seems to be more effective than anterior callosotomy for drop seizures.[108,127] Callosotomy may be considered as an early treatment option in patients for whom drop seizures are particularly problematic (e.g., if the patient suffers repeated injury from drop seizures, or is wheelchair-bound due to drop seizure frequency).[128] Re-evaluation with EEG and MRI is recommended before and after callosotomy to detect any changes resulting from the procedure (e.g., development of focal seizures). Although VNS is less invasive than callosotomy, it still involves a surgical procedure and its use will therefore largely depend on patient/parent/caregiver choice. It can take time for the effects of VNS to become apparent, with further improvement over time. The decision as to when VNS should be used will depend on a variety of factors, including age, time since LGS diagnosis, and whether the patient has been experiencing troublesome or intolerable AEs with ASM treatment. VNS can be used in conjunction with ASM therapy and with callosotomy.

6.1.2 | Patients with LGS that has evolved from another type of epilepsy (e.g., IESS)

Many patients will either have been treated with ASM therapy to initially control seizures before LGS diagnosis or will have developed LGS having progressed over time from another epilepsy syndrome, such as IESS.[129] Most patients presenting with apparently generalized seizures will already be receiving VPA. If this is the case, then the treatment algorithm shown in Figure 1 can be followed (i.e., adding LTG as the first adjunctive therapy if VPA does not provide adequate seizure control, etc.). If the patient is already being treated with another first-line ASM (typically LEV), then VPA therapy should be initiated and the other therapy tapered off and discontinued. Thereafter, the treatment algorithm is the same as for a newly diagnosed patient (Figure 1).

If the patient is being treated with more than one ASM and neither is VPA, then VPA therapy should be initiated and one of the previous ASMs tapered off and discontinued. If seizure control is inadequate after introducing VPA and the second ASM is not LTG, then LTG should be initiated and the other non-VPA ASM tapered off and discontinued. Thereafter, the treatment algorithm is the same as for a newly diagnosed patient (Figure 1).

6.2 | Older patients with established LGS

It is recommended that patients with established LGS undergo review by a neurologist with established experience in the treatment of complex epilepsies and drug interactions on at least an annual basis, comprising a thorough reassessment of their diagnosis (in terms of epilepsy syndrome and etiology) and treatment plan. The diagnosis should be re-evaluated by repeating investigations conducted at initial diagnosis and/or conducting investigations that were previously not undertaken (EEG [including sleep-EEG, if possible], MRI, and genetic testing), to confirm the diagnosis and help elucidate etiology. Results of previous investigations should be reviewed alongside those of new investigations. Since the patient's clinical and EEG features continue to evolve, a diagnosis other than LGS may become apparent and treatment should be adapted accordingly. Clinicians should always be alert to the possibility that the diagnosis may change and be vigilant to the possibility of treatable etiologies. Clinicians should also be aware that the "classic" EEG features (SSW complexes) may evolve and/or disappear later in the disease course.[29,130] Loss of these features does not necessarily mean that the patient no longer has LGS, but this possibility must be considered alongside the reassessment of other clinical/EEG features. Genetic counseling should be offered, if appropriate. EEG should be repeated whenever there are any concerns over diagnosis, signs of deterioration, or suspected NCSE. It is mandatory to have a recent baseline EEG for comparison, in case the patient presents with suspected NCSE in the future.

6.3 | Management of NCSE

Up to 75% of patients with LGS experience episodes of NCSE.[10] Its clinical presentation can vary from a mild confusional state to a coma.[131] However, presentation in this population may be quite subtle; by definition, NCSE is a change in behavior and EEG from baseline.[132] The diminished responsiveness may be insidious in its onset, and therefore may be missed. A high index of suspicion is therefore required on the part of the physician, particularly if a previous baseline EEG is not available for comparison.[132] Patients with LGS should be regularly assessed for the development of possible NCSE, including EEG, and, where possible, EEG results should be compared with a baseline recording.[131] Expert advice may be required to confirm or refute an NCSE diagnosis.

Treatment for NCSE is less urgent than for convulsive status epilepticus and overtreatment should be avoided since most patients do not require aggressive treatment (expert opinion). Patients should not be admitted to intensive care to induce anesthetic treatment, since this could potentially be more harmful to the patient than the condition itself. NCSE should be treated with CLB and/or steroids (expert opinion), although there is currently no evidence for any agent or dosing regimen,[76] and the use of steroids varies according to local protocol. High-dose intravenous VPA can also be effective,[133] and there is emerging data that FFA can be used as a treatment option for NCSE in patients with LGS.[134] The goal of treatment is to return the EEG to its pre-NCSE baseline pattern, and treatment should be optimized with ongoing review. Patients with NCSE should be referred for specialist advice and/or EEG monitoring.

7 | OTHER CONSIDERATIONS FOR LGS MANAGEMENT

7.1 | Comorbidities

The lives of patients with LGS are affected not only by frequent and disabling seizures but also by a range of comorbidities, including physical disability, cognitive impairment, behavioral problems (e.g., hyperactivity, aggressiveness, and autistic traits), and sleep disturbances.[1,9,32] Mobility is further restricted by

the protective equipment (e.g., wheelchair, helmet, and faceguard) that is often required to prevent seizure-related injury.[1] Management of comorbidities in LGS is a key aspect of care. This should include careful consideration when choosing ASM treatment, not only with regard to potential drug interactions with medications used to treat comorbidities but also because some ASMs may themselves cause or worsen certain comorbidities (such as cognitive impairment and depression).[1]

7.2 | Impact on QoL

The QoL of patients with LGS is severely impaired throughout their lives.[1,9,20,116] The ability to participate in everyday activities is restricted by the physical impact of LGS and the need for protective equipment, and cognitive and behavioral problems often prevent mainstream school attendance.[1,9] As individuals progress into adulthood, LGS affects their independence, ability to work, personal relationships and social participation.[1,9] LGS also severely affects the QoL of parents, caregivers and other family members.[20,116–118]

7.3 | Transition from childhood to adulthood

Transitioning from pediatric to adult care is difficult for both patients and families but provides an important opportunity for reassessment of all aspects of care, including re-evaluation of a patient's etiology, EEG features and pharmacological and non-pharmacological treatment options.[1,9] The multidisciplinary needs of the patient and family should also be reassessed at this time (e.g., social care support, provision of community/residential care, and psychiatric support).[1,9] The transition process can be facilitated by attendance at transition/teenager clinics.[1,9,135,136] All patients should be reviewed by a neurologist at least annually.[1]

7.4 | Need for multidisciplinary care

LGS requires a multidisciplinary, individualized approach to care throughout the course of life, which addresses the patient's medical, psychological, educational, and social needs, as well as the needs of their caregiver/family.[1,137] Ideally, these multidisciplinary needs should be re-assessed annually, and include the patient's health and social care needs, their potential need for institutionalization (particularly in adulthood), and support for the caregiver/family.[1]

8 | FUTURE DIRECTIONS

Despite difficulties in identifying and characterizing LGS, future efforts should be made to formalize clinical trial strategies to provide clearer evidence of the potential benefits of therapeutic interventions, including non-pharmacological treatments (e.g., cell therapy and gene therapy) in addition to ASMs. Eligibility criteria for study entry should be consistent with the current definition of LGS,[3] and EEG features should be clearly defined and standardized between study centers.[10] Inclusion of patients with non-specific DEEs with stratification based on DEE type might also be explored. Duration of epilepsy prior to enrollment should be taken into account since this can impact the presentation of characteristic LGS features.[10] Improved early identification of LGS may allow subgroups of patients to be defined, such as those transitioning to LGS from IESS and those with early advanced neurophysiological changes; similarly, early elucidation of etiology (e.g., genetic pathogenic variants and structural abnormalities) may allow better understanding of the potential benefits of an intervention in different etiology subgroups. In terms of study design, the use of an active comparator would be preferable to comparing with a placebo,[10] and the choice of active comparator could be based on the next standard ASM in the treatment algorithm presented in Figure 1. Treatment duration should ideally be at least 6 months and studies could be designed to assess the effects of an intervention in subgroups with different LGS etiologies. The number and type of concomitant therapies and rescue therapies allowed during the trial should be specified.[10] The types of seizures assessed in the trial should also be specified and, in addition to seizure reduction, assessment of the severity of seizures, duration of seizures, number of days without seizures, and improvement/worsening of specific seizure types could be considered as potential study endpoints.[10,138,139] Specific EEG biomarkers that may serve as indicators of treatment response or disease progression in LGS could be explored; these might involve changes in spike–wave index, reduction in nocturnal paroxysmal fast activity, spectral power, or other quantitative measures.[10] Additional endpoints should also be considered, such as the effects of an intervention on QoL, cognition, and behavior.[10]

Future directions in LGS management are likely to focus increasingly on the use of personalized/precision medicine; for example, the potential utility of genetic testing, including pharmacogenomics to convey information for patients sensitive to severe adverse drug reactions.[140–142] If LGS is known to be caused by an underlying disease then this disease should be specifically treated whenever possible; for example, using everolimus

to treat tuberous sclerosis complex[143] and GAP activity toward RAGs (GATOR) complex 1 (GATOR 1) epilepsies[144]; resective surgery for patients with cortical dysplasia due to disheveled EGL-10 and pleckstrin domain-containing protein 5 (*DEPDC5*) variants[145]; and the use of KDT and avoidance of VPA in patients with mitochondrial diseases.[146–151] It is also likely that existing pharmacological agents may be repurposed for use in LGS, as has been the case for FFA.[152]

ACKNOWLEDGMENTS

The development of this publication (including support for publication fees) was funded by a grant from UCB. Editorial support for the preparation of the manuscript was provided by John Scopes of m*X*m Medical Communications and funded by the grant. The opinions expressed in this article are the independent consensus views of the authors and have not been influenced by third-party sponsorship.

CONFLICT OF INTEREST STATEMENT

Stéphane Auvin is Deputy Editor for *Epilepsia*. He has served as a consultant or received honoraria for lectures from Angelini Pharma, Biocodex, Biomarin, Eisai, Encoded, Grintherapeutics, Jazz Pharma, Neuraxpharm, Nutricia, Proveca, Stoke, Supernus, Takeda, UCB Pharma, and Xenon. He has been an investigator for clinical trials for Eisai, Marinus, Proveca, Takeda, and UCB Pharma. Alexis Arzimanoglou is Editor-in-Chief Emeritus for *Epileptic Disorders*, educational journal of the ILAE, and Associate Editor for the *European Journal of Paediatric Neurology*. He has served as a consultant or received honoraria for lectures from Biocodex, Biomarin, Eisai, Jazz Pharma, Neuraxpharm, Nutricia, Takeda, and UCB Pharma. He has been an investigator for clinical trials and/or DMC member for Eisai, Jazz Pharma, and UCB Pharma. His Institution received educational grants from UCB Pharma, GW, and the Caixa Foundation. In his mission as Coordinator of the ERN EpiCARE, his Institution received funding from the European Commission. Mercè Falip has served as a consultant or received honoraria for lectures from Angelini Pharma, Eisai, Esteve, Jazz Pharma, Livanova, Neuraxpharm, and UCB Pharma. She has served as an investigator for clinical trials for UCB Pharma, Jazz Pharma, and Angelini Pharma. Pasquale Striano is the Associate Editor for *Epilepsia Open* and *Epileptic Disorders*. He has served as a consultant or received honoraria for lectures from Angelini Pharma, Biocodex, Biomarin, Eisai, Encoded, Jazz Pharma, Neuraxpharm, Proveca, Takeda, and UCB Pharma. He has been an investigator for clinical trials for Longboard, Takeda, and UCB Pharma. He is supported by #NEXTGENERATIONEU (NGEU) and funded by the Ministry of University and Research (MUR), National Recovery and Resilience Plan (NRRP), project MNESYS (PE0000006)—A Multiscale Integrated Approach to the Study of the Nervous System in Health and Disease (DN. 1553 11.10.2022). This work was also supported by the Italian Ministry of Health, RICERCA CORRENTE 2024. J Helen Cross has served as an investigator for clinical trials for UCB, Jazz, Stoke Therapeutics, and Ultragenyx. She has served on advisory boards for Biocodex, UCB, and Jazz Pharmaceuticals and spoken in educational symposia for Biocodex, UCB, Nutricia, and Jazz; all remuneration has been paid to her department. She is in receipt of grants from Engineering and Physical Sciences Research Council (UK), Epilepsy Research UK, Great Ormond Street Hospital Children's Charity, National Institute for Health and Care Research. All research is supported by the National Institute of Health Research Biomedical Research Centre at Great Ormond Street Hospital.

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.

ORCID

Stéphane Auvin https://orcid.org/0000-0003-3874-9749
Alexis Arzimanoglou https://orcid.org/0000-0002-7233-2771
Mercè Falip https://orcid.org/0000-0002-8738-5083
Pasquale Striano https://orcid.org/0000-0002-6065-1476
J. Helen Cross https://orcid.org/0000-0001-7345-4829

REFERENCES

1. 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.
2. Scheffer IE, Berkovic S, Capovilla G, Connolly MB, French J, Guilhoto L, et al. ILAE classification of the epilepsies: position paper of the ILAE Commission for Classification and Terminology. Epilepsia. 2017;58:512–21.
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. European Medicines Agency. Epidyolex (cannabidiol) summary of product characteristics. [Cited 2019 Oct 4]. Available from: https://www.ema.europa.eu/en/documents/product-information/epidyolex-epar-product-information_en.pdf
5. US Food and Drug Administration. Epidiolex (cannabidiol) prescribing information. [Cited 2020 Jun]. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/210365Orig1s011lbl.pdf
6. European Medicines Agency. Fintepla (fenfluramine) summary of product characteristics. [Cited 2021 Jan 8]. Available

from: https://www.ema.europa.eu/en/documents/product-information/fintepla-epar-product-information_en.pdf
7. UCB. Fintepla (fenfluramine) prescribing information. [Cited 2023 Dec]. Available from: https://www.ucb-usa.com/fintepla-prescribing-information.pdf
8. Scheffer IE, Liao J. Deciphering the concepts behind "epileptic encephalopathy" and "developmental and epileptic encephalopathy". Eur J Paediatr Neurol. 2020;24:11–4.
9. Kerr M, Kluger G, Philip S. Evolution and management of Lennox-Gastaut syndrome through adolescence and into adulthood: are seizures always the primary issue? Epileptic Disord. 2011;13(Suppl 1):S15–S26.
10. Arzimanoglou A, French J, Blume WT, Cross JH, Ernst JP, Feucht M, et al. Lennox-Gastaut syndrome: a consensus approach on diagnosis, assessment, management, and trial methodology. Lancet Neurol. 2009;8:82–93.
11. 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.
12. 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.
13. EuroEPINOMICS-RES Consortium EPGP, Epi4K Consortium. De novo mutations in synaptic transmission genes including DNM1 cause epileptic encephalopathies. Am J Hum Genet. 2014;95:360–70.
14. Epilepsy Phenome/Genome Project Epi4K Consortium. Copy number variant analysis from exome data in 349 patients with epileptic encephalopathy. Ann Neurol. 2015;78:323–8.
15. Monfrini E, Borellini L, Zirone E, Yahya V, Mauri E, Molisso MT, et al. GABRB1-related early onset developmental and epileptic encephalopathy: clinical trajectory and novel de novo mutation. Epileptic Disord. 2023;25:867–73.
16. Matsuishi T, Yoshino M, Tokunaga O, Katafuchi Y, Yamashita F. Subacute necrotizing encephalomyelopathy (Leigh disease): report of a case with Lennox-Gastaut syndrome. Brain Dev. 1985;7:500–4.
17. Leuzzi V, Mastrangelo M, Battini R, Cioni G. Inborn errors of creatine metabolism and epilepsy. Epilepsia. 2013;54:217–27.
18. Chevrie JJ, Aicardi J. Childhood epileptic encephalopathy with slow spike-wave. A statistical study of 80 cases. Epilepsia. 1972;13:259–71.
19. Arzimanoglou A, Guerrini R, Aicardi J. Lennox-Gastaut syndrome. In: Arzimanoglou A, Guerrini R, Aicardi J, editors. Aicardi's epilepsy in children. 3rd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2004. p. 38–50.
20. 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.
21. 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;65:1224–39.
22. Arzimanoglou A, Resnick T. All children who experience epileptic falls do not necessarily have Lennox-Gastaut syndrome... But many do. Epileptic Disord. 2011;13(Suppl 1):S3–S13.
23. Genton P, Guerrini R, Dravet C. The Lennox-Gastaut sydrome. In: Meinardi H, editor. Handbook of clinical neurology: the epilepsies. Amsterdam: Elsevier; 2000. p. 211–22.
24. Rantala H, Putkonen T. Occurrence, outcome, and prognostic factors of infantile spasms and Lennox-Gastaut syndrome. Epilepsia. 1999;40:286–9.
25. Beaumanoir A, Dravet C. The Lennox-Gastaut syndrome. In: Roger J, Bureau M, Dravet C, editors. Epileptic syndromes in infancy, childhood and adolescence. London: John Libbey; 1992. p. 115–32.
26. Geoffroy G, Lassonde M, Delisle F, Décarie M. Corpus callosotomy for control of intractable epilepsy in children. Neurology. 1983;33:891–7.
27. Dravet C, Roger J, Bureau M, Dalla BB. Myoclonic epilepsies in childhood. In: Akimoto H, Kazamatsuri H, Seino M, editors. Advances in epileptology, XIIIth epilepsy international symposium. New York, NY: Raven Press; 1982. p. 135–40.
28. Gastaut H, Dravet C, Loubier D. Evolution clinique et prognostic du syndrome de Lennox-Gastaut. In: Lugaresi E, Pazzaglia P, Tassinari CA, editors. Evolution and prognosis of epilepsies. Bologna: Aulo Gaggi; 1973. p. 133–54.
29. 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.
30. Hughes JR, Patil VK. Long-term electro-clinical changes in the Lennox-Gastaut syndrome before, during, and after the slow spike-wave pattern. Clin Electroencephalogr. 2002;33:1–7.
31. Wolff M, Johannesen KM, Hedrich UBS, Masnada S, Rubboli G, Gardella E, et al. Genetic and phenotypic heterogeneity suggest therapeutic implications in SCN2A-related disorders. Brain. 2017;140:1316–36.
32. van Rijckevorsel K. Treatment of Lennox-Gastaut syndrome: overview and recent findings. Neuropsychiatr Dis Treat. 2008;4:1001–19.
33. Aicardi J, Chevrie JJ. Atypical benign partial epilepsy of childhood. Dev Med Child Neurol. 1982;24:281–92.
34. Doose H, Hahn A, Neubauer BA, Pistohl J, Stephani U. Atypical "benign" partial epilepsy of childhood or pseudolennox syndrome. Part II: family study. Neuropediatrics. 2001;32:9–13.
35. Jahngir MU, Ahmad MQ, Jahangir M. Lennox-Gastaut syndrome: in a nutshell. Cureus. 2018;10:e3134.
36. Strzelczyk A, Schubert-Bast S. Expanding the treatment landscape for Lennox-Gastaut syndrome: current and future strategies. CNS Drugs. 2021;35:61–83.
37. Resnick T, Sheth RD. Early diagnosis and treatment of Lennox-Gastaut syndrome. J Child Neurol. 2017;32:947–55.
38. Bourgeois BF, Douglass LM, Sankar R. Lennox-Gastaut syndrome: a consensus approach to differential diagnosis. Epilepsia. 2014;55(Suppl 4):4–9.
39. Pujar S, Cross JH. Diagnosis of Lennox-Gastaut syndrome and strategies for early recognition. Expert Rev Neurother. 2024;24:383–9.
40. Sills GJ. Pharmacological diversity amongst approved and emerging antiseizure medications for the treatment of developmental and epileptic encephalopathies. Ther Adv Neurol Disord. 2023;16:17562864231191000.
41. Reyhani A, Özkara Ç. The unchanging face of Lennox-Gastaut syndrome in adulthood. Epilepsy Res. 2021;172:106575.
42. 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.

43. Sullivan J, Benítez A, Roth J, Andrews JS, Shah D, Butcher E, et al. A systematic literature review on the global epidemiology of Dravet syndrome and Lennox–Gastaut syndrome: prevalence, incidence, diagnosis, and mortality. Epilepsia. 2024;65:1240–63.
44. Brigo F, Jones K, Eltze C, Matricardi S. Anti-seizure medications for Lennox-Gastaut syndrome. Cochrane Database Syst Rev. 2021;4:CD003277.
45. Knupp KG, Scheffer IE, Ceulemans B, Sullivan JE, Nickels KC, Lagae L, et al. Efficacy and safety of fenfluramine for the treatment of seizures associated with Lennox-Gastaut syndrome. JAMA Neurol. 2022;79:554–64.
46. Datapharm. Epilim (sodium valproate) summary of product characteristics. [Cited Jan 23]. Available from: https://www.medicines.org.uk/emc/medicine/6781
47. European Medicines Agency. Lamictal (lamotrigine) summary of product characteristics. [Cited Jan 23]. Available from: https://www.ema.europa.eu/en/documents/referral/lamictal-article-30-referral-annex-i-ii-iii_en.pdf
48. Motte J, Trevathan E, Arvidsson JF, Barrera MN, Mullens EL, Manasco P. Lamotrigine for generalized seizures associated with the Lennox-Gastaut syndrome. Lamictal Lennox-Gastaut Study Group. N Engl J Med. 1997;337:1807–12.
49. European Medicines Agency. Inovelon (rufinamide) summary of product characteristics. [Cited Jan 23]. Available from: https://www.ema.europa.eu/en/documents/product-information/inovelon-epar-product-information_en.pdf
50. Glauser T, Kluger G, Sachdeo R, Krauss G, Perdomo C, Arroyo S. Rufinamide for generalized seizures associated with Lennox–Gastaut syndrome. Neurology. 2008;70:1950–8.
51. European Medicines Agency. Topamax (topiramate) summary of product characteristics. [Cited Jan 23]. Available from: https://www.ema.europa.eu/en/documents/referral/topamax-article-30-referral-annex-i-ii-iii_en.pdf
52. Sachdeo RC, Glauser TA, Ritter F, Reife R, Lim P, Pledger G. A double-blind, randomized trial of topiramate in Lennox-Gastaut syndrome. Topiramate YL Study Group. Neurology. 1999;52:1882–7.
53. US Food and Drug Administration. Onfi (clobazam) prescribing information. [Cited Jan 23]. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/202067s006,203993s008lbl.pdf
54. Ng YT, Conry JA, Drummond R, Stolle J, Weinberg MA. Randomized, phase III study results of clobazam in Lennox-Gastaut syndrome. Neurology. 2011;77:1473–81.
55. Isojarvi J, Lee D, Peng G, Sperling MR. Clobazam-treated patients with Lennox-Gastaut syndrome experienced fewer seizure-related injuries than placebo patients during trial OV-1012. Epilepsia. 2016;57:e113–e116.
56. Datapharm. Frisium (clobazam) Summary of Product Characteristics. [Cited Jan 23]. Available from: https://www.medicines.org.uk/emc/product/1574/smpc#gref
57. Lee EH, Yum MS, Choi HW, Ko TS. Long-term use of clobazam in Lennox-Gastaut syndrome: experience in a single tertiary epilepsy center. Clin Neuropharmacol. 2013;36:4–7.
58. Gunning B, Mazurkiewicz-Bełdzińska M, Chin RFM, Bhathal H, Nortvedt C, Dunayevich E, et al. Cannabidiol in conjunction with clobazam: analysis of four randomized controlled trials. Acta Neurol Scand. 2021;143:154–63.
59. US Food and Drug Administration. Felbatol (felbamate) prescribing information. [Cited Jan 23]. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/020189s027lbl.pdf
60. Ugale V, Deshmukh R, Lokwani D, Narayana Reddy P, Khadse S, Chaudhari P, et al. GluN2B subunit selective N-methyl-D-aspartate receptor ligands: democratizing recent progress to assist the development of novel neurotherapeutics. Mol Divers. 2023;28:1–28.
61. Felbamate Study Group in Lennox-Gastaut Syndrome. Efficacy of felbamate in childhood epileptic encephalopathy (Lennox-Gastaut syndrome). N Engl J Med. 1993;328:29–33.
62. Devinsky O, Patel AD, Cross JH, Villanueva V, Wirrell EC, Privitera M, et al. Effect of cannabidiol on drop seizures in the Lennox–Gastaut syndrome. N Engl J Med. 2018;378:1888–97.
63. Thiele EA, Marsh ED, French JA, Mazurkiewicz-Beldzinska M, Benbadis SR, Joshi C, et al. Cannabidiol in patients with seizures associated with Lennox-Gastaut syndrome (GWPCARE4): a randomised, double-blind, placebo-controlled phase 3 trial. Lancet. 2018;391:1085–96.
64. Sills GJ, Brodie MJ. Update on the mechanisms of action of antiepileptic drugs. Epileptic Disord. 2001;3:165–72.
65. Arzimanoglou A, Brandl U, Cross JH, Gil-Nagel A, Lagae L, Landmark CJ, et al. Epilepsy and cannabidiol: a guide to treatment. Epileptic Disord. 2020;22:1–14.
66. Patel AD, Mazurkiewicz-Bełdzińska M, Chin RF, Gil-Nagel A, Gunning B, Halford JJ, et al. Long-term safety and efficacy of add-on cannabidiol in patients with Lennox-Gastaut syndrome: results of a long-term open-label extension trial. Epilepsia. 2021;62:2228–39.
67. Malaca S, Gottardi M, Pigliasco F, Barco S, Cafaro A, Amadori E, et al. UHPLC-MS/MS analysis of cannabidiol and its metabolites in serum of patients with resistant epilepsy treated with CBD formulations. Pharmaceuticals (Basel). 2021;14:630.
68. Nabbout R, Arzimanoglou A, Auvin S, Berquin P, Desurkar A, Fuller D, et al. Retrospective chart review study of use of cannabidiol (CBD) independent of concomitant clobazam use in patients with Lennox-Gastaut syndrome or Dravet syndrome. Seizure. 2023;110:78–85.
69. Iannone LF, Arena G, Battaglia D, Bisulli F, Bonanni P, Boni A, et al. Results from an Italian expanded access program on cannabidiol treatment in highly refractory Dravet syndrome and Lennox–Gastaut syndrome. Front Neurol. 2021;12:673135.
70. Knupp KG, Scheffer IE, Ceulemans B, Sullivan J, Nickels KC, Lagae L, et al. Fenfluramine provides clinically meaningful reduction in frequency of drop seizures in patients with Lennox-Gastaut syndrome: interim analysis of an open-label extension study. Epilepsia. 2023;64:139–51.
71. Correction to "fenfluramine provides clinically meaningful reduction in frequency of drop seizures in patients with Lennox-Gastaut syndrome: interim analysis of an open-label extension study". Epilepsia. 2024;65:2179.
72. Valls Carbó A, Beltrán Á, Sánchez-Miranda Román I, Cabal B, Gómez-Porro P, Aledo-Serrano Á, et al. What have we learned from the real-world efficacy of FFA in DS and LGS? A post-marketing study in clinical practice. Epilepsy Behav. 2024;151:109620.
73. Halford JJ, Sperling MR, Arkilo D, Asgharnejad M, Zinger C, Xu R, et al. A phase 1b/2a study of soticlestat as adjunctive

therapy in participants with developmental and/or epileptic encephalopathies. Epilepsy Res. 2021;174:106646.
74. Hahn CD, Jiang Y, Villanueva V, Zolnowska M, Arkilo D, Hsiao S, et al. A phase 2, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of soticlestat as adjunctive therapy in pediatric patients with Dravet syndrome or Lennox-Gastaut syndrome (ELEKTRA). Epilepsia. 2022;63:2671–83.
75. Takeda. Press release: Takeda announces phase 3 topline results for soticlestat (TAK-935) in patients with Dravet Syndrome and Lennox-Gastaut Syndrome. 2024. [cited 2024 Aug 05]. Available from: https://www.takeda.com/newsroom/newsreleases/2024/soticlestat-drevat-syndrom-phase3-results/
76. Korinthenberg R, Bast T, Haberlandt E, Stephani U, Strzelczyk A, Rücker G. Efficacy and safety of corticosteroids and ACTH in epileptic syndromes beyond infantile epileptic spasms syndrome (IESS): a systematic review and meta-analysis. Epilepsia. 2024;65:1155–75.
77. Buchman AL. Side effects of corticosteroid therapy. J Clin Gastroenterol. 2001;33:289–94.
78. Kothare S, Kluger G, Sachdeo R, Williams B, Olhaye O, Perdomo C, et al. Dosing considerations for rufinamide in patients with Lennox–Gastaut syndrome: phase III trial results and real-world clinical data. Seizure. 2017;47:25–33.
79. Striano P, McMurray R, Santamarina E, Falip M. Rufinamide for the treatment of Lennox-Gastaut syndrome: evidence from clinical trials and clinical practice. Epileptic Disord. 2018;20:13–29.
80. Balagura G, Riva A, Marchese F, Verrotti A, Striano P. Adjunctive rufinamide in children with Lennox-Gastaut syndrome: a literature review. Neuropsychiatr Dis Treat. 2020;16:369–79.
81. ClinicalTrials.gov. Study of perampanel as adjunctive treatment for inadequately controlled seizures associated with Lennox-Gastaut Syndrome (NCT02834793). [cited 2024Aug 08]. Available from: https://clinicaltrials.gov/study/NCT02834793
82. Kim HJ, Kim SH, Kang HC, Lee JS, Chung HJ, Kim HD. Adjunctive levetiracetam treatment in pediatric Lennox-Gastaut syndrome. Pediatr Neurol. 2014;51:527–31.
83. You SJ, Kang HC, Kim HD, Lee HS, Ko TS. Clinical efficacy of zonisamide in Lennox-Gastaut syndrome: Korean multicentric experience. Brain Dev. 2008;30:287–90.
84. Auvin S, Dozieres B, Ilea A, Delanoë C. Use of perampanel in children and adolescents with Lennox-Gastaut syndrome. Epilepsy Behav. 2017;74:59–63.
85. Matricardi S, Cesaroni E, Bonanni P, Foschi N, D Aniello A, Di Gennaro G, et al. Long-term effectiveness of add-on perampanel in patients with Lennox-Gastaut syndrome: a multicenter retrospective study. Epilepsia. 2023;64:e98–e104.
86. Crespel A, Tang NPL, Macorig G, Gelisse P, Genton P. Open-label, uncontrolled retrospective study of perampanel in adults with Lennox-Gastaut syndrome. Seizure. 2020;75:66–9.
87. Falcicchio G, Lattanzi S, Negri F, de Tommaso M, La Neve A, Specchio N. Treatment with Cenobamate in adult patients with Lennox–Gastaut syndrome: a case series. J Clin Med. 2022;12:129.
88. 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.
89. Skrobas U, Duda P, Bryliński Ł, Drożak P, Pelczar M, Rejdak K. Ketogenic diets in the management of Lennox-Gastaut Syndrome-review of literature. Nutrients. 2022;14:4977.
90. 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.
91. Morris GL 3rd, Gloss D, Buchhalter J, Mack KJ, Nickels K, Harden C. Evidence-based guideline update: vagus nerve stimulation for the treatment of epilepsy. Neurology. 2013;81:1453–9.
92. Karceski S. Vagus nerve stimulation and Lennox-Gastaut syndrome: a review of the literature and data from the VNS patient registry. CNS Spectr. 2001;6:766–70.
93. 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.
94. 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 Dev. 2008;30:195–9.
95. Orosz I, McCormick D, Zamponi N, Varadkar S, Feucht M, Parain D, et al. Vagus nerve stimulation for drug-resistant epilepsy: a European long-term study up to 24 months in 347 children. Epilepsia. 2014;55:1576–84.
96. Dibué M, Greco T, Spoor JKH, Tahir Z, Specchio N, Hänggi D, et al. Vagus nerve stimulation in patients with Lennox-Gastaut syndrome: a meta-analysis. Acta Neurol Scand. 2021;143:497–508.
97. Ben-Menachem E. Vagus-nerve stimulation for the treatment of Epilepsy. Lancet Neurol. 2002;1:477–82.
98. Shahwan A, Bailey C, Maxiner W, Harvey AS. Vagus nerve stimulation for refractory epilepsy in children: more to VNS than seizure frequency reduction. Epilepsia. 2009;50:1220–8.
99. Douglass LM, Salpekar J. Surgical options for patients withLennox-Gastaut syndrome. Epilepsia. 2014;55(Suppl 4):21–8.
100. Lancman G, Virk M, Shao H, Mazumdar M, Greenfield JP, Weinstein S, et al. Vagus nerve stimulation vs. corpus callosotomy in the treatment of Lennox-Gastaut syndrome: a meta-analysis. Seizure. 2013;22:3–8.
101. Cukiert A, Cukiert CM, Burattini JA, Lima AM, Forster CR, Baise C, et al. Long-term outcome after callosotomy or vagus nerve stimulation in consecutive prospective cohorts of children with Lennox-Gastaut or Lennox-like syndrome and non-specific MRI findings. Seizure. 2013;22:396–400.
102. Kwan SY, Lin JH, Wong TT, Chang KP, Yiu CH. A comparison of seizure outcome after callosotomy in patients with Lennox-Gastaut syndrome and a positive or negative history for west syndrome. Seizure. 2006;15:552–7.
103. Liang S, Zhang S, Hu X, Zhang Z, Fu X, Jiang H, et al. Anterior corpus callosotomy in school-aged children with Lennox-Gastaut syndrome: a prospective study. Eur J Paediatr Neurol. 2014;18:670–6.
104. Ferreira Soares D, Pires de Aguiar PH. Callosotomy vs Vagus Nerve stimulation in the treatment of Lennox-Gastaut Syndrome: a systematic review wwith meta-analysis. Neuromodulation. 2023;26:518–28.

105. Roth J, Bergman L, Weil AG, Brunette-Clement T, Weiner HL, Treiber JM, et al. Added value of corpus callosotomy following vagus nerve stimulation in children withLennox–Gastautsyndrome: a multicenter, multinational study. Epilepsia. 2023;64:3205–12.
106. Hamdi H, Boissonneau S, Valton L, McGonigal A, Bartolomei F, Regis J. Radiosurgical corpus Callosotomy for intractable epilepsy: retrospective long-term safety and efficacy assessment in 19 patients an review of the literature. Neurosurgery. 2023;93:156–67.
107. Tao JX, Satzer D, Issa NP, Collins J, Wu S, Rose S, et al. Stereotactic laser anterior corpus callosotomy for Lennox-Gastaut syndrome. Epilepsia. 2020;61:1190–200.
108. Baumgartner JE, Ajmal FQ, Baumgartner ME, Seo JH, Hussain A, Westerveld M, et al. Palliation for catastrophic nonlocalizing epilepsy: a retrospective case series of complete corpus callosotomy at a single institution. J Neurosurg Pediatr. 2023;32:553–61.
109. Son BC, Shon YM, Choi JG, Kim J, Ha SW, Kim SH, et al. Clinical outcome of patients with deep brain stimulation of the Centromedian thalamic nucleus for refractory epilepsy and location of the active contacts. Stereotact Funct Neurosurg. 2016;94:187–97.
110. Velasco F, Velasco AL, Velasco M, Jiménez F, Carrillo-Ruiz JD, Castro G. Deep brain stimulation for treatment of the epilepsies: the centromedian thalamic target. Acta Neurochir Suppl. 2007;97:337–42.
111. Warren AEL, Dalic LJ, Bulluss KJ, Thevathasan W, Archer JS. The optimal target and connectivity for deep brain stimulation in Lennox-Gastaut Syndrome. Ann Neurol. 2022;92:61–74.
112. Dalic LJ, Warren AEL, Bulluss KJ, Thevathasan W, Roten A, Churilov L, et al. DBS of thalamic Centromedian nucleus for Lennox-Gastaut syndrome (ESTEL trial). Ann Neurol. 2022;91:253–67.
113. Alanazi RF, Alkhani AM. Management of Lennox-Gastaut syndrome with deep brain stimulation: a systematic literature review. Neurosciences (Riyadh). 2022;27:216–20.
114. Aungaroon G. Does deep brain stimulation work in Lennox-Gastaut syndrome? Well...it depends. Epilepsy Curr. 2022;22:222–4.
115. Camfield P, Camfield C. Long-term prognosis for symptomatic (secondarily) generalized epilepsies: a population-based study. Epilepsia. 2007;48:1128–32.
116. 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.
117. Gibson PA. Lennox-Gastaut syndrome: impact on the caregivers and families of patients. J Multidiscip Healthc. 2014;7:441–8.
118. 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.
119. Riva A, Coppola A, Bonaventura CD, Elia M, Ferlazzo E, Gobbi G, et al. An Italian consensus on the management of Lennox-Gastaut syndrome. Seizure. 2022;101:134–40.
120. 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.
121. Xian J, Parthasarathy S, Ruggiero SM, Balagura G, Fitch E, Helbig K, et al. Assessing the landscape of STXBP1-related disorders in 534 individuals. Brain. 2022;145:1668–83.
122. Lattanzi S, Trinka E, Striano P, Rocchi C, Salvemini S, Silvestrini M, et al. Highly purified cannabidiol for epilepsy treatment: a systematic review of epileptic conditions beyond Dravet syndrome and Lennox-Gastaut syndrome. CNS Drugs. 2021;35:265–81.
123. Besag FMC, Vasey MJ, Chin RFM. Current and emerging pharmacotherapy for the treatment of Lennox-Gastaut syndrome. Expert Opin Pharmacother. 2023;24:1249–68.
124. Pellock JM. Felbamate in epilepsy therapy: evaluating the risks. Drug Saf. 1999;21:225–39.
125. Strzelczyk A, Schubert-Bast S. Psychobehavioural and cognitive adverse events of anti-seizure medications for the treatment of developmental and epileptic encephalopathies. CNS Drugs. 2022;36:1079–111.
126. Kossoff EH, Laux LC, Blackford R, Morrison PF, Pyzik PL, Hamdy RM, et al. When do seizures usually improve with the ketogenic diet? Epilepsia. 2008;49:329–33.
127. Kasasbeh AS, Smyth MD, Steger-May K, Jalilian L, Bertrand M, Limbrick DD. Outcomes after anterior or complete corpus callosotomy in children. Neurosurgery. 2014;74:17–28.
128. Hansen D, Shandley S, Olaya J, Hauptman J, Auguste K, Ostendorf AP, et al. A multi-center comparison of surgical techniques for corpus Callosotomy in pediatric drug-resistant epilepsy. Epilepsia. 2023;65:422–9.
129. Muir AM, Myers CT, Nguyen NT, Saykally J, Craiu D, De Jonghe P, et al. Genetic heterogeneity in infantile spasms. Epilepsy Res. 2019;156:106181.
130. 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.
131. Akman CI. Nonconvulsive status epilepticus and continuous spike and slow wave of sleep in children. Semin Pediatr Neurol. 2010;17:155–62.
132. Walker M, Cross H, Smith S, Young C, Aicardi J, Appleton R, et al. Nonconvulsive status epilepticus: epilepsy research foundation workshop reports. Epileptic Disord. 2005;7:253–96.
133. Uberall MA, Trollmann R, Wunsiedler U, Wenzel D. Intravenous valproate in pediatric epilepsy patients with refractory status epilepticus. Neurology. 2000;54:2188–9.
134. Strzelczyk A, Becker H, Tako L, Hock S, Hattingen E, Rosenow F, et al. Fenfluramine for the treatment of status epilepticus: use in an adult with Lennox–Gastaut syndrome and literature review. Neurol Res Pract. 2024;6:10.
135. Jurasek L, Ray L, Quigley D. Development and implementation of an adolescent epilepsy transition clinic. J Neurosci Nurs. 2010;42:181–9.
136. Camfield P, Camfield C, Pohlmann-Eden B. Transition from pediatric to adult epilepsy care: a difficult process marked by medical and social crisis. Epilepsy Curr. 2012;12:13–21.
137. Arzimanoglou A, Resnick T. Diagnosing and treating epileptic drop attacks, atypical absences and episodes of nonconvulsive status epilepticus. Epileptic Disord. 2011;13(Suppl 1):S1–S2.
138. Auvin S, Williams B, McMurray R, Kumar D, Perdomo C, Malhotra M. Novel seizure outcomes in patients with

Lennox-Gastaut syndrome: post hoc analysis of seizure-free days in rufinamide study 303. Epilepsia Open. 2019;4:275–80.
139. Auvin S, Nortvedt C, Fuller DS, Sahebkar F. Seizure-free days as a novel outcome in patients with Lennox-Gastaut syndrome: post hoc analysis of patients receiving cannabidiol in two randomized controlled trials. Epilepsia. 2023;64:1812–20.
140. Bayat A, Bayat M, Rubboli G, Møller RS. Epilepsy syndromes in the first year of life and usefulness of genetic testing for precision therapy. Genes (Basel). 2021;12:1051.
141. Billakota S, Andresen JM, Gay BC, Stewart GR, Fedorov NB, Gerlach AC, et al. Personalized medicine: vinpocetine to reverse effects of GABRB3 mutation. Epilepsia. 2019;60:2459–65.
142. Riva A, Roberti R, D'Onofrio G, Vari MS, Amadori E, De Giorgis V, et al. A real-life pilot study of the clinical application of pharmacogenomics testing on saliva in epilepsy. Epilepsia Open. 2023;8:1142–50.
143. Johannessen Landmark C, Potschka H, Auvin S, Wilmshurst JM, Johannessen SI, Kasteleijn-Nolst Trenité D, et al. The role of new medical treatments for the management of developmental and epileptic encephalopathies: novel concepts and results. Epilepsia. 2021;62:857–73.
144. Moloney PB, Kearney H, Benson KA, Costello DJ, Cavalleri GL, Gorman KM, et al. Everolimus precision therapy for the GATOR1-related epilepsies: a case series. Eur J Neurol. 2023;30:3341–6.
145. McGinley C, Teti S, Hofmann K, Schreiber JM, Cohen NT, Gaillard WD, et al. Seizure control outcomes following resection of cortical dysplasia in patients with DEPDC5 variants: a systematic review and individual patient data analysis. Neuropediatrics. 2024;55:1–8.
146. Kang HC, Lee YM, Kim HD, Lee JS, Slama A. Safe and effective use of the ketogenic diet in children with epilepsy and mitochondrial respiratory chain complex defects. Epilepsia. 2007;48:82–8.
147. Staretz-Chacham O, Pode-Shakked B, Kristal E, Abraham SY, Porper K, Wormser O, et al. The effects of a ketogenic diet on patients with dihydrolipoamide dehydrogenase deficiency. Nutrients. 2021;13:3523.
148. Thorburn DR, Rahman J, Rahman S. Mitochondrial DNA-associated Leigh syndrome and NARP. In: Adam MP, Feldman J, Mirzaa GM, Pagon RA, Wallace SE, Bean LJH, et al., editors. GeneReviews(®). Seattle, WA: University of Washington, Seattle Copyright © 1993–2024, University of Washington, Seattle. GeneReviews is a registered trademark of the University of Washington, Seattle. All rights reserved; 1993.
149. Lee IC, Chiang KL. Clinical diagnosis and treatment of Leigh syndrome based on SURF1: genotype and phenotype. Antioxidants (Basel). 2021;10:1950.
150. Lopriore P, Gomes F, Montano V, Siciliano G, Mancuso M. Mitochondrial epilepsy, a challenge for neurologists. Int J Mol Sci. 2022;23:13216.
151. Mancuso M, Lopriore P, Lamperti C, Klopstock T, Rahman S, Licchetta L, et al. Current management of primary mitochondrial disorders in EU countries: the European reference networks survey. J Neurol. 2024;271:835–40.
152. Balagura G, Cacciatore M, Grasso EA, Striano P, Verrotti A. Fenfluramine for the treatment of Dravet syndrome and Lennox-Gastaut syndrome. CNS Drugs. 2020;34:1001–7.

How to cite this article: Auvin S, Arzimanoglou A, Falip M, Striano P, Cross JH. Refining management strategies for Lennox–Gastaut syndrome: Updated algorithms and practical approaches. Epilepsia Open. 2024;00:1–22. https://doi.org/10.1002/epi4.13075