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Expert opinion: Proposed diagnostic and treatment algorithms for Lennox–Gastaut syndrome in adult patients

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A B S T R A C T

Lennox–Gastaut syndrome (LGS) is a severe developmental epileptic encephalopathy diagnosed in childhood that persists through adolescence and into adulthood. While the characteristics of LGS in pediatric patients are well defined, including “drop attacks”, interictal slow spike and wave electroencephalogram (EEG) activity, and intellectual disability, these features can evolve over time, and different EEG activities may be present in adult patients with LGS. This may result in missed diagnoses in these patients and subsequent challenges for the adequate treatment of their seizures. Based on discussions held during the LGS Transition of Care advisory board meeting and thereafter, we developed proposed diagnostic and treatment algorithms for LGS in adult patients.

We highlight readily available assessments to facilitate diagnosis of LGS, based on past medical history and physical examination. The LGS diagnostic algorithm recommends that clinicians consider the occurrence of wider seizure types and abnormal EEG activities to be potentially indicative of LGS. Seizure types may include atypical absence seizures, myoclonic seizures, focal seizures, and tonic–clonic seizures, and EEG may demonstrate background slowing, focal or multifocal epileptiform discharges, and diffuse fast rhythms during sleep, among other activities. Extended EEG during sleep and video-EEG should be used in equivocal cases.

Treatment of LGS in adult patients should incorporate both antiseizure drug (ASD) therapy and nonpharmacologic approaches. Frequent reassessment of patients is considered a central aspect. ASDs were categorized based on order of preference for use in the treatment of LGS; Tier 1 comprises recommended first-line ASDs, and includes valproate, clobazam, lamotrigine, rufinamide, topiramate, and cannabidiol. Other treatment options include diet, neurostimulation, and surgical approaches.

Developments with the potential to improve diagnosis in the future include genetic screening, while novel ASDs and advances in neurostimulation techniques may provide valuable treatment options. These algorithms should be frequently revisited to incorporate improved techniques and therapies.

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Abbreviations: AAN, American Academy of Neurology; ASD, antiseizure drug; BCP, birth control pill; BRV, brivaracetam; CBD, cannabidiol; CBZ, carbamazepine; CLB, clorazepate; CNZ, clonazepam; DBS, deep brain stimulation; DZP, diazepam; EEG, electroencephalogram; FBM, felbamate; FRITC, focal to bilateral tonic–clonic; FDA, Food and Drug Administration; GBP, gabapentin; GTC, generalized tonic–clonic; HSV, herpes simplex virus; ID, intellectual disability; KD, ketogenic diet; LCM, lacosamide; LEV, levetiracetam; LGS, Lennox–Gastaut syndrome; LTG, lamotrigine; OXC, oxcarbazepine; PBT, phenobarbital; PDD, pervasive developmental disorder; PER, perampanel; PGB, pregabalin; PHT, phenytoin; RNS, responsive neurostimulation; RUF, rufinamide; SCN1A, sodium channel neuronal type I, alpha subunit; SCP, spastic cerebral palsy; SE, status epilepticus; SGE, symptomatic generalized epilepsy; SSW, slow spike and wave; STP, stiripentol; TC, tonic–clonic; TGB, tiagabine; TMD, trimethadione; TPM, topiramate; TS, tuberous sclerosis; V-EEG, video-electroencephalogram; VGT, vigabatrin; VNS, vagus nerve stimulation; VPA, valproate; ZNS, zonisamide.

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1. Introduction

Lennox–Gastaut syndrome (LGS) is a severe developmental epileptic encephalopathy [1,2], with onset usually occurring between the ages of 3 and 5 years, and typically before the age of 8 years [3]. Diagnosis of LGS still relies upon the presentation of the classical triad of characteristics, which include: multiple seizure types (including tonic, atonic, and atypical absence seizures) [2,4]; abnormal electroencephalogram (EEG) activity (consisting primarily of an interictal pattern of diffuse slow spike and wave (SSW) activity, occurring during wakefulness) [2,4]; and intellectual disability [2]. Gastaut originally described this triad of characteristics in 1966 [2], and these historical criteria now present challenges for the effective and reliable diagnosis of LGS in adult patients, since the classic signs of LGS can evolve in patients over time [1,4,5]. This evolution could potentially result in differences in EEG activities emerging in patients with LGS with increasing age, as demonstrated in a patient with LGS and tuberous sclerosis in Fig. 1, and the occurrence of seizure types beyond those most commonly associated with LGS. Consequently, adult neurologists may look for signs of LGS that are no longer present in adult patients; therefore, patients could be incorrectly characterized as having generalized epilepsy, rather than receiving a correct diagnosis of LGS. In addition, many patients may present to an adult neurologist for the first time, providing little or no medical history from infancy, further complicating the detection of any preceding signs of LGS that may have occurred during childhood [5].

American Academy of Neurology (AAN) and American Epilepsy Society (AES) treatment guidelines for LGS, based on the assessment of evidence available in the literature (during 1987–2015), indicate that lamotrigine, topiramate, and rufinamide are established as effective in treating LGS; based on clinical experience, clobazam is also established as an effective treatment for LGS [6,7]. These four antiseizure drugs (ASDs) have each received approval from the Food and Drug Administration (FDA) for the treatment of seizures associated with LGS [8–11] and along with valproate, which has not been approved for the treatment of LGS, comprise the most commonly used medications for the treatment of LGS [4]. Since the publication of the AAN and AES treatment guidelines, cannabidiol has also received FDA approval for the treatment of seizures associated with LGS [12]. Felbamate is considered to be effective in the treatment of LGS; however, in the context of LGS and due to its unfavorable safety profile, felbamate is only recommended for use in patients over 4 years of age who are unresponsive to the primary ASDs [13]. However, long-term cessation or control of seizures with ASD treatment may not be a realistic goal for most patients with LGS due to the refractory nature of the seizures.

Fig. 1. EEGs demonstrating activities from a patient with LGS and tuberous sclerosis at the ages of (A) 13 years and (B) 25 years. EEG, electroencephalogram; LGS, Lennox–Gastaut syndrome.
A rudimentary diagnostic framework was created to facilitate discussion and treating LGS in adult patients. During the advisory board meeting, these cases highlight the challenges associated with diagnosing LGS. A summary of these cases is provided in Table 1. Notably, behavioral issues may be exacerbated in patients with intellectual disabilities during the transition to adult services, as a result of anxiety experienced in leaving a pediatric neurologist with whom they have developed a relationship over time for an unfamiliar adult neurologist, and also due to disruption to an established routine [16–18]. Adolescent patients can face challenges receiving treatment from pediatric care services, which may prefer to move patients on to adult services rather than retain them in pediatric care due to limited resources and a shortage of pediatric neurologists [4,16,19]. However, adult healthcare services may not always be suitably prepared for patients with intellectual disabilities, may have a significantly different culture and approach to care compared with pediatric services, and will not usually accept patients aged under 18 years [4,16]. Further issues can arise from the changes occurring in an adolescent patient’s life surrounding their sexual maturity, and social, financial, and legal status [16].

While the management of LGS has been reviewed previously [4], approaches for the diagnosis and treatment of LGS specifically in adolescent and adult patients are not as well established, potentially due to the belief that LGS is a childhood syndrome. The underdiagnosis of LGS in adult patients needs to be addressed in order to prevent patients from receiving ineffective and unsuitable medications, and therefore a broader definition of LGS and improved awareness of additional indicators of LGS may reduce missed diagnoses. In addition, current treatment algorithms are considered suboptimal for adults newly diagnosed with LGS and for adult patients with LGS undergoing a transition of care, especially as many patients with LGS are refractory to ASDs, with reported rates of patients experiencing seizures that persist long-term ranging from 66 to 100% [20–23]. In order to discuss the development of the proposed diagnostic and treatment algorithms for LGS in adult patients, the LGS Transition of Care advisory board convened in November 2017, with the objectives of supporting a smoother transition of care and facilitating reliable and effective diagnosis and treatment of LGS in adult patients. Here, we present the two proposed algorithms that emerged from these discussions, both of which have been further developed subsequent to the advisory board meeting.

2. Proposed diagnostic algorithm for LGS in adult patients

2.1. Development of the LGS diagnostic algorithm

Given that the previous definition of LGS was considered outdated, attendees of the advisory board devised a diagnostic algorithm based upon their own clinical experience and expert opinion. In addition, attendees each developed two case studies prior to the meeting, which described real patients or hypothetical or composite cases. The first was based on an adult or adolescent patient with LGS, who was either in the process of transitioning from pediatric care or had recently transitioned from pediatric care, and the second was based on an adult patient with LGS who had already transitioned. Cases were reviewed and one case from each advisor was presented at the advisory board meeting. A summary of these cases is provided in Table 1. Notably, these cases highlight the challenges associated with diagnosing and treating LGS in adult patients. During the advisory board meeting, a rudimentary diagnostic framework was created to facilitate discussions around the core criteria that are essential for making a clinical diagnosis of LGS in adults. The primary focus of discussion was to identify readily available assessments to facilitate the diagnosis of LGS in adult patients with refractory seizures and in a community setting.

Since the advisory board meeting, advisors continued to discuss the diagnostic algorithm to produce the version presented here.

2.2. Proposed diagnostic algorithm for LGS in adult patients

Readily available assessments to form the basis of the diagnostic algorithm were identified, which can be applied on presentation of an adult patient with refractory seizures. These assessments include past medical history, physical examination, and review of medical records (Fig. 2).

Although the occurrence of multiple seizure types during childhood is already understood to be indicative of LGS [3], a wider array of seizure types should be considered when making assessments based on a patient’s medical history. The presence or history of two or more seizure types that are often resistant to medical treatment may contribute to a diagnosis of LGS. These seizure types include, but are not limited to, drop attacks (including tonic, atonic, and myoclonic atonic seizures), atypical absence seizures, myoclonic seizures, focal (partial) seizures, and tonic–clonic seizures (including focal to bilateral tonic–clonic [secondarily generalized] seizures and generalized-onset tonic–clonic [primary generalized tonic–clonic] seizures).

Age at onset of LGS symptoms should also be considered. Although Gastaut originally noted that a range from 1 to 6 years of age was generally the most common period for the onset of symptoms [2], our proposed diagnostic algorithm is consistent with more contemporary guidelines that recognize that onset usually occurs between 3 and 5 years of age, and typically occurs before 8 years of age (Table 2) [3]. Childhood onset of developmental delays and cognitive impairment should also be regarded as potential signs of LGS, and these may occur alongside behavioral disturbances, such as aggressiveness, autistic traits, and hyperactivity [24].

Findings from physical examination of an adult patient with refractory seizures may reveal neurological deficits or could inform the etiology of their refractory seizures. Indicators from physical examination that may suggest a diagnosis of LGS include the presence of symptoms of neurocutaneous syndromes (such as tuberous sclerosis), hemiparesis, quadriparesis, and cognitive impairment.

While the absence of medical records, case summaries, and referral letters from pediatric neurologists may be problematic, the review of such documentation, where available, may contribute towards the diagnosis of LGS. A possible history of West syndrome should be investigated as this can often develop into LGS, as reported in 34% of patients with West syndrome by Camfield et al. [25], and it may be regarded as an antecedent syndrome to LGS. However, a history of West syndrome should not be considered a requirement for a diagnosis of LGS.

In adults with LGS, EEG assessment has shown slow background activity, diffuse slow spike–wave discharges during wakefulness, and bursts of diffuse fast rhythms during sleep [26]. In equivocal cases, where a diagnosis of LGS is not conclusive after readily available assessments have been conducted, a routine EEG should be performed to distinguish abnormal activity that may be indicative of LGS, including SSW activity (Fig. 3A). However, given that EEG activities in patients with LGS commonly evolve as patients mature, SSW activity may no longer be present in adult patients. Instead, other abnormal activities may be detected and should be recognized as possible signs of LGS. These include, but are not limited to, diffuse bilateral background slowing, focal spike and wave discharges, multifocal epileptiform discharges, generalized polyspike and wave discharges, and generalized paroxysmal fast discharges (Fig. 3B–F). When a diagnosis of LGS remains uncertain after EEG, admission of the patient to an epilepsy monitoring unit for a multihour EEG with sleep features should be considered [26].

Based on this algorithm, if a diagnosis of LGS in an adult patient is probable or possible, treatment of LGS should be initiated. While the proposed treatment algorithm is outlined later in this paper, in patients where multiple ASDs fail, referral to a tertiary center for video-EEG and/or to an epileptologist is recommended. A summary to compare the criteria
<table>
<thead>
<tr>
<th>Patient</th>
<th>Age, years</th>
<th>Summary of patient history</th>
<th>EEG/V-EEG activities</th>
<th>Treatments Current</th>
<th>Past</th>
<th>Course of care/challenges</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>33</td>
<td>Recurrent seizures since SE episode at 5 months old; infantile spasms at 9 months, and hypsarrhythmia; cerebral palsy; frequent falling</td>
<td>Generalized slowing; multi-focal epileptiform discharges; generalized slow spike–wave discharges</td>
<td>VPA, RUF, LEV, CBZ, ZNS, VPA, VNS</td>
<td></td>
<td>Challenges: Limited medical records at first visit</td>
</tr>
<tr>
<td>2</td>
<td>32</td>
<td>Decreased muscle tone; episodes of myoclonus and several drop attacks per day; developmental delay; never developed speech</td>
<td>Generalized slowing; epileptiform discharges; slow spike and wave discharges; tonic seizures with generalized discharges</td>
<td>RUF, VPA, VPA, ZNS, PHT, PVC, TPM</td>
<td></td>
<td>Challenges: Lack of records from pediatric neurologist – only records for previous 1–2 years received from the general neurologist; relied on recollection of patient’s mother and description of initial seizures; mother reluctant to consider VNS and some medication changes; aggressive behavior</td>
</tr>
<tr>
<td>3</td>
<td>18</td>
<td>PDD, TS, LGS</td>
<td>Tonic seizures (generalized paroxysmal fast activity) with focal features; multiple independent spike foci; multifocal delta slowing; asymmetric diffuse polymorphic delta-theta slowing; frontal rhythmic delta activity</td>
<td>BRV, LCM, PER, VPA, VGT, VNS</td>
<td></td>
<td>Challenges: Mitochondrial encephalopathy, epilepsy; complex transitions and re-challenging with medications require trust between patient/caregivers and providers; comprehensive epilepsy team to seamlessly continue care, full-time psychiatry services</td>
</tr>
<tr>
<td>4</td>
<td>16</td>
<td>Mitochondrial disorder, LGS, developmental delay. Referred to palliative care; hospitalized for increase in tonic seizures, lethargy, inability to eat</td>
<td>Tonic seizures with spike–wave discharge followed by generalized paroxysmal fast activity; generalized slow spike–wave discharges; electrodecremental discharges in sleep; background disorganization and slowing</td>
<td>VPA, CLB, LEV, STP, VGT, ZNS</td>
<td></td>
<td>Challenges: Separated parents: comorbidities; bond with pediatric team (years); transitional care team required at both ends</td>
</tr>
<tr>
<td>5</td>
<td>17</td>
<td>ID; HSV meningeno-encephalitis at 1 month; aspiration pneumonia; SCP; LGS</td>
<td>Background slowing with slow spike and wave discharges, more prominent in sleep</td>
<td>VPA, CLB, LEV, VNS</td>
<td></td>
<td>Treatment plans: Adult epileptologist identified and detailed clinical summary provided; continue current regimen and consider PER or FBMT; consider VPA.</td>
</tr>
<tr>
<td>6</td>
<td>22</td>
<td>SGE from 1 year of age; ID; SCP; prematurity birth; LGS; (+) SCN1A mutation</td>
<td>Background slowing with multifocal spikes; slow spike and wave discharges</td>
<td>LEV, (+ LTG)</td>
<td>PHT, OXC</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>48</td>
<td>Intractable seizures (from 2 years); developmental delay; LGS diagnosis at 8 years</td>
<td>Multifocal sharp waves; complex partial seizure; multiple tonic type seizures</td>
<td>LEV, LTG, VPA, CBZ, RUF, PHT, VPA, CNZ</td>
<td></td>
<td>Recommendations from pediatric epileptologist: LTG may worsen patients seizures and related injuries – patient more alert, talkative, and in better mood</td>
</tr>
<tr>
<td>8</td>
<td>36</td>
<td>Febrile SE; residual left hemiparesis; developmental delay; LGS diagnosis at 6 years</td>
<td>Diffuse background slowing with multifocal sharp discharges; electrodecremental discharges; generalized asymmetric slow spike and wave activity</td>
<td>LEV, LTG, VPA, CNZ, VNS, CRB, ZNS, PHT, VPA, CNZ, VNS</td>
<td></td>
<td>Challenges: ID; intractable epilepsy, severe developmental disability; failed multiple regimens</td>
</tr>
</tbody>
</table>
for diagnosis based on this proposed algorithm compared with those of the classical LGS diagnostic criteria based on Gastaut et al. (1966) is provided in Table 2 [2].

### 2.3. Future directions for the diagnosis of LGS in adult patients

Given the challenges associated with diagnosing LGS in adult patients, the implementation of novel assessments to facilitate swifter diagnoses is desirable, as this may allow treatment with appropriate ASDs to be initiated sooner and for more targeted treatments to be identified. In addition, earlier diagnosis of LGS can help the medical provider in discussing the prognosis with families and caregivers. One possibility to improve upon current approaches to LGS diagnosis is the development of a multigene panel to be tested. Such screening would not be able to rule out a diagnosis of LGS, as structural or cryptogenic etiologies unrelated to genetic mutations cannot be eliminated by such approaches [1]. However, a significant proportion of the estimated 25% of patients with LGS of a cryptogenic etiology may benefit from an additional diagnostic assessment based on genetic testing [30,31].

### 3. A proposed treatment algorithm for LGS in adult patients

#### 3.1. Development of the LGS treatment algorithm

As previous treatment algorithms were considered to be suboptimal for informing treatment decisions for adult patients with LGS, coupled with its multiple etiologies (structural, metabolic, and genetic) [32], attendees of the advisory board meeting, further discussions have been held to revise the treatment algorithm and account for recent developments, such as the approval of cannabidiol by the FDA for the treatment of LGS [12].

#### 3.2. Proposed treatment algorithm for LGS in adult patients

Based on the discussions to develop the treatment algorithm, frequent reassessment and follow-up of adult patients with LGS is recommended as a cornerstone of the proposed treatment algorithm (Fig. 4). Reassessment may occur at least once every three, six, or 12 months, and this should be determined based on seizure frequency, changes in medication, and other medical needs. The management of behavioral symptoms should also be considered when assessing treatment options. Patients with vagus nerve stimulation (VNS) implants may require more frequent visits for programming.

Antiseizure drug polytherapy is recommended alongside complementary non-ASD interventions; because of the refractory nature of the seizures associated with LGS, successful treatment with ASD monotherapy is rare. FDA-approved ASDs specifically indicated for the treatment of LGS have been categorized into Tier 1 of ASDs in the treatment algorithm, and these currently include clobazam, lamotrigine, rufinamide, topiramate, and cannabidiol [8,9,11,12]. Based on the most common survey responses, valproate was also included in Tier 1 and was chosen as the top ASD for the treatment of seizures associated with LGS, despite not being FDA-approved for the treatment of LGS [33]. Reasons for the frequent use of valproate in the treatment of seizures associated with LGS include the wealth of clinical experience of its use to treat LGS, cost effectiveness, its effect as a mood stabilizer on comorbidities, and the existence of multiple formulations. Lamotrigine is also recommended as first-line therapy for the treatment of LGS, while clobazam and rufinamide were the most commonly selected ASDs for add-on therapy. To date, only one formulation of cannabidiol has received FDA approval for the treatment of patients with LGS aged 2 years and older, and other pharmaceutical formulations are currently still under investigation. In addition, while artisanal preparations of cannabidiol are available, none are approved for the treatment of LGS. Based on the approval of cannabidiol (June 2018) and the relative lack of clinical experience of its use in the treatment of LGS compared with the other Tier 1 ASDs, cannabidiol has been included in the LGS treatment algorithm as the last-choice Tier 1 ASD [12].

Tier 2 ASDs include those which are commonly selected for the treatment of seizures associated with LGS, and include levetiracetam, perampanel, and zonisamide [34–36]. Lacosamide and brivaracetam are considered potentially valuable in the treatment of LGS but lack systematic trial data to support their efficacy and/or associated safety concerns. An additional group of ASDs to be avoided in the treatment of seizures associated with LGS was also defined. The case studies described earlier in relation to the diagnostic algorithm were also used to inform the development of the treatment algorithm. Nonpharmacologic interventions complementary to ASD treatments were also discussed and included in the development of the treatment algorithm. Since the advisory board meeting, further discussions have been held to revise the treatment algorithm and account for recent developments, such as the approval of cannabidiol by the FDA for the treatment of LGS [12].

### Table 1 (continued)

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (years)</th>
<th>Summary of patient history</th>
<th>EEG/V-EEG activities</th>
<th>Treatments</th>
<th>Course of care/challenges</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient 9</td>
<td>32</td>
<td>Infantile spasms (9 months); LGS (3 years)</td>
<td>Previous: Slow spike and wave</td>
<td>LCM, LEV, VNS</td>
<td>Lacosamide and valproate treatment; Tier 2 ASDs included; Patient had no long-term response to any ASDs; full-time care by mother and/or father</td>
</tr>
<tr>
<td>Patient 10</td>
<td>18</td>
<td>Cognitive delay; hypotonia; crying; aspiration pneumonia; fever; weight loss; LGS (2 years)</td>
<td>Previous: bilateral frontal spikes; multifocal epileptiform spikes</td>
<td>LTC, OXC, LEV, CBD, ZNS, CNZ, VPA</td>
<td>Challenges: Anxiety over switching from pediatric neurologist to adult neurologist</td>
</tr>
</tbody>
</table>

Services available: Direct nurse to nurse and doctor to doctor care |
the treatment of seizures associated with LGS should be considered carefully. Cenobamate has recently been approved by the FDA for the treatment of focal (partial) seizures [42], and on this basis, has been included in Tier 3 of the treatment algorithm. This positioning of cenobamate will be reviewed as further evidence becomes available from clinical trials and clinical experience.

Antiseizure drugs that should be avoided in the treatment of LGS were also identified. These include ASDs less frequently used in the treatment of LGS and ASDs that have the potential to exacerbate certain seizure types. This category includes carbamazepine, eslicarbazepine, gabapentin, oxcarbazepine, phenytoin, pregabalin, and vigabatrin [9,39,43–47]. It is important to observe any potential adverse effects relating to behavioral dysfunction following the selection of an ASD for the treatment of LGS.

Complementary interventions that may be applied in parallel with ASD therapy include nonpharmacologic treatments, community services, and psychosocial approaches. The implementation of a ketogenic diet is a common approach for the control of refractory seizures, and its use for the treatment of seizures associated with LGS in pediatric patients has been reported elsewhere [48]. Assessment of the ketogenic diet is important to monitor for potential adverse effects, such as weight loss, electrolyte disturbances, and liver function abnormalities.

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**Fig. 2.** Summary of the proposed LGS diagnostic algorithm for adult patients with refractory seizures proposed by the LGS Transition of Care advisory board. *Including focal to bilateral tonic–clonic (secondarily generalized) seizures and generalized onset tonic–clonic (primary generalized tonic–clonic) seizures. EEG, electroencephalogram; LGS, Lennox–Gastaut syndrome; V-EEG, video-electroencephalogram.
diet in adult patients with LGS suggests that it is a useful therapy to contribute towards seizure control, although sustained seizure freedom may not be consistently achieved [21]. The modified Atkins diet, a variant of the ketogenic diet, may also be beneficial for adult patients with LGS [21], as it is better tolerated and can be initiated as an outpatient.

Vagus nerve stimulation has been investigated as a treatment for adult patients with drug-resistant epilepsy and in pediatric patients with LGS [49,50]; however, its application in adult patients with LGS has not been as extensively studied. Based on the assessment of available studies, AAN guidelines recommend that VNS should be considered for the treatment of seizures associated with LGS [51]. The latest iteration of VNS (SenTiva®, LivaNova) allows detection of seizure activity by time (during sleep vs wakefulness) and in prone vs supine positions. This can be used as a surrogate marker to assess risk of sudden unexpected death in epilepsy. In addition, if confronted with predominant nocturnal seizures, the nocturnal duty cycle can be preferentially increased over the daytime cycle. Deep brain stimulation (DBS) also presents a potential non-pharmacologic treatment [52]; however, there is currently limited experience of DBS in adult patients with LGS.

Other more invasive surgical interventions that may be considered for the treatment of seizures associated with LGS include resective surgery and corpus callosotomy [53]. While resective surgery may be suitable for selected patients with surgically accessible epileptogenic foci, corpus callosotomy and VNS are potential options for the treatment of tonic seizures in non-lesional patients [53–55].

Table 2
Comparison of the classical criteria used for the diagnosis of LGS and criteria based on the proposed LGS diagnostic algorithm.

<table>
<thead>
<tr>
<th>Presence of intellectual disability</th>
<th>Classical LGS diagnostic criteria</th>
<th>Proposed LGS diagnostic criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>Yes</td>
<td>Drop attacks (tonic, atonic, and myoclonic atonic seizures)</td>
</tr>
<tr>
<td>Seizure types</td>
<td>Drop attacks (tonic and atonic seizures)</td>
<td>Atypical absence seizures Myoclonic seizures Focal (partial) seizures Tonic–clonic seizures</td>
</tr>
<tr>
<td>EEG activity</td>
<td>Slow spike and wave</td>
<td>Multifocal spike and wave discharges Generalized polyspike and wave discharges Generalized paroxysmal fast discharges</td>
</tr>
<tr>
<td>Other considerations</td>
<td>Age at onset: Generally between 1 and 6 years</td>
<td>Between 3 and 5 years, typically before 8 years</td>
</tr>
<tr>
<td></td>
<td>Physical examination: –</td>
<td>May reveal neurological deficits or etiology of seizures</td>
</tr>
</tbody>
</table>

EEG, electroencephalogram; LGS, Lennox–Gaustad syndrome.

4. A note on nomenclature

Finally, it should be noted that there has been a move in the medical community away from the naming of conditions and diseases after individuals, particularly considering information that has later come to light on Hans Asperger’s and Frederich Wegener’s links to the Nazi regime. This has led to the renaming of Wegener's developments in the field, assessments in future may also include genetic testing. Ultimately, the transition of care from pediatric care to adult care requires a significant level of trust to be developed between the patient, caregivers, and providers, and the difficulties experienced during this transition may be allayed by establishing transition clinics and implementing a multidisciplinary management team [16].

3.3. Redefining goals of treatment during transition

Changes in the features of LGS during the period of transition call for reassessment of treatment goals, and as quality of life becomes more important in the longer term than measurements of seizure outcome, goals should be tailored to include measures of behavioral symptoms and cognition. For example, the International Classification of Function, Health, and Disability (ICF) have developed a model that provides examples of the different aspects of global assessment that should be considered across the lifespan, and is applicable to patients aged 4, 12, and 35 years. In the ICF model, assessments related to the functioning of the patient are described as three dimensions: body function or structure (e.g., seizure freedom and cognitive improvements), activity and participation (e.g., improvement in self-independence and relationships), and environmental factors (e.g., burden on the family or partner). However, this classification was intended for assessment of stable disorders and its application in patients with LGS requires further investigation [3].

3.4. Future directions in the treatment of LGS in adult patients

As further clinical experience is accumulated for the current therapies included in the treatment algorithm, and new therapies that may be suitable for the treatment of LGS are in development, revisions to the proposed LGS treatment algorithm will be required. Several medications have the potential to be introduced into the treatment algorithm in the future, depending on their performance in the treatment of LGS and their safety profiles. Fenfluramine, which was previously approved as an appetite suppressant, does not have approval for the treatment of epilepsy. However, in pediatric patients, fenfluramine has demonstrated efficacy for the treatment of seizures associated with Dravet syndrome in phase III studies (NCT02682927 and NCT02826863) [56] and for the treatment of seizures with LGS in an open-label pilot study (NCT02655198) [57]. An ongoing phase III study (NCT03355209) is assessing the efficacy of fenfluramine in pediatric and adult patients with LGS and is estimated to complete in December 2019 [58]. Based on a case series of patients with childhood-onset epilepsies including LGS and Dravet syndrome, loraserin, which also does not have FDA approval for the treatment of these syndromes [59], may have some efficacy in controlling motor seizures in these patients [60]. Other drugs under investigation for the treatment of LGS include carisbamate (phase I: NCT03731715) and TAK-935 (phase II: NCT03635073 and NCT03650452) [61–63].

Responsive neurostimulation (RNS) may also present an effective therapeutic approach for the treatment of LGS in adult patients; however, RNS is not currently approved for the treatment of LGS and further understanding on which patients may benefit from RNS is required before any recommendations can be made as part of the LGS treatment algorithm [64,65]. A potential advantage of RNS is in its provision of chronic electrocorticography, which may be valuable as a diagnostic application [65].
granulomatosis as ‘granulomatosis with polyangiitis’, whereas Asperger’s syndrome is no longer considered a separate condition, but has been incorporated into the broader category of autism spectrum disorder [66]. Similarly, there may be an argument for the phasing out of the term ‘Lennox–Gastaut syndrome’, considering that the condition was named after the neurologist William G. Lennox (along with Henri Gastaut) and the former’s support of eugenics [67]. However, ultimately this is an issue for consideration by the scientific and patient communities moving forwards.

5. Conclusions

Based on our clinical experience and following discussions held during and since the LGS Transition of Care advisory board in November 2017, we have proposed diagnostic and treatment algorithms for the management of adult patients with LGS. Several readily available assessments have been identified to facilitate diagnosis of LGS in adult patients, and these form the basis of the diagnostic algorithm. Many adults may present with refractory seizures but without a previous diagnosis of LGS; the widening of the criteria used for the diagnosis of LGS, and raised awareness of a broader group of indicators of LGS, should reduce the frequency of missed diagnoses, and allow adult patients diagnosed with LGS to receive appropriate treatment.

The treatment of LGS in adult patients or in patients undergoing a transition from pediatric care to adult care can be challenging, as patients are often refractory to ASDs, and current treatment algorithms are considered suboptimal. Here, we have proposed a treatment algorithm to outline therapies that should be considered for the treatment of adult patients with LGS. Antiseizure drugs considered to be effective in the treatment of LGS in adult patients have been placed

Table 3

<table>
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<tr>
<th>ASD</th>
<th>Check ✓ all that apply</th>
<th>ASD dosage</th>
<th>Yes</th>
<th>No</th>
<th>If “No”, provide reason(s) and action taken</th>
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<td>Clobazam</td>
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<td>Zonisamide</td>
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<td>Other (describe)</td>
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ASD, antiseizure drug; LGS, Lennox–Gastaut syndrome.
into Tiers 1 and 2; the recommended first-line medications are valproate, clobazam, lamotrigine, rufinamide, topiramate, and cannabidiol. Complementary interventions, to be used in parallel with ASD therapy, include nonpharmacologic treatments, community services, and psychosocial approaches.

Limitations of these algorithms include their development being based on our own clinical experience and case studies, rather than on a systematic review of clinical trial data. However, a previous systematic review was unable to determine the most effective treatment for LGS, due to the low number of randomized clinical trials in LGS and heterogeneity across the trials that have been conducted [14]; given this, the review and discussion of case studies can provide valuable evidence to inform treatment decisions.

Lastly, we have also identified ongoing developments that may result in updates to the diagnostic and treatment algorithms. Further advances in genetic testing for LGS may present innovative tools to facilitate more effective diagnosis, while additional treatment options could include novel ASDs and neurostimulation therapies. Based on this, we encourage ongoing discussion to reassess the recommendations of the diagnostic and treatment algorithms, to improve outcomes in this highly refractory patient population.

**Author contributions**

All authors were participants of the advisory board and were involved in the reviewing and approval of the manuscript, and in the decision to submit the article for publication. All authors also confirm accountability for the accuracy and integrity of the work.

**Declaration of competing interest**

Georgia Montouris has served on advisory boards for Eisai and SK Life Science, and has served on a safety board for UCB Pharma. Sami Aboumatar has served on advisory boards and/or has carried out consulting work for Eisai and Sunovion. David Burdette has served on advisory boards for Eisai and SK Life Science; has received speaker bureau honoraria from Eisai, Greenwich Biosciences, NeuroPace, Sunovion, and UCB Pharma; and has received research grant support from Eisai, NeuroPace, and Zogenix. Sanjeev Kothare and Ruben Kuzniecky have served on an advisory board for Eisai. William Rosenfeld has served on advisory boards for Eisai and SK Life Science; serves as a consultant for SK Life Science; has received speaker bureau honoraria from Eisai, Sunovion, and UCB Pharma; and has received research grant support from Greenwich Biosciences, Neuriris, Ovid Therapeutics, SK Life Science, and others.

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![Fig. 4. Summary of the proposed treatment algorithm for adult patients with LGS proposed by the LGS Transition of Care advisory board. Consider patient factors when selecting ASDs.](image-url)

Fig. 4. Summary of the proposed treatment algorithm for adult patients with LGS proposed by the LGS Transition of Care advisory board. Consider patient factors when selecting ASDs. FDA-approved for LGS. Cannabidiol is included as the last-choice Tier 1 ASD treatment. At present, only one formulation of cannabidiol is FDA-approved for the treatment of LGS; other pharmaceutical formulations are currently under investigation. Cenobamate is included in Tier 3, but may be re-positioned in future based on trial data and clinical experience. There is limited experience of deep brain stimulation in adults with LGS. ASD, antiseizure drug; FDA, Food and Drug Administration; LGS, Lennox–Gastaut syndrome.
Science, Takeda, and UCB Pharma. Steve Chung has served on advisory boards for Eisai, SK Life Science, Sunovion, and UCB Pharma; has received speaker bureau honoraria from Eisai, Lundbeck, Sunovion, and UCB Pharma; and has received research grant support from SK Life Science and UCB Pharma.

Acknowledgments

The advisory board was convened and funded by Eisai Inc. Members of the advisory board were selected based on the following criteria: adult neurologists/epileptologists who have expertise in treating patients with epilepsy and have patients who meet the criteria for LGS. The role of Eisai in the advisory board was to bring together neurologists/epileptologists with the necessary expertise to provide input on the transition of care and treatment of patients with LGS. The specific objectives of the meeting were as follows: 1. Obtain expert insight on the differences between pediatric and adult patients with LGS; 2. Gain expert feedback on key attributes necessary for adult neurologists to successfully identify and treat patients with LGS; 3. Develop an outline for a proposed diagnostic algorithm for LGS in adults and a proposed treatment algorithm for LGS in adults; 4. Obtain advisor feedback on educational needs with respect to transition of care in LGS; and 5. Obtain advisory feedback on data gaps in the treatment of adults with seizures associated with LGS.

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The contents of this paper have previously been presented at the 72nd Annual Meeting of the American Epilepsy Society, New Orleans, LA, USA, November 30–December 4, 2018. The treatment algorithm has also been presented at the 71st Annual Meeting of the American Academy of Neurology, Philadelphia, PA, USA, May 4–10, 2019.

References


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