Neurotherapeutics (2023) 20:1255–1262
https://doi.org/10.1007/s13311-023-01397-x

CURRENT PERSPECTIVES

Lennox-Gastaut Syndrome: Current Treatments, Novel Therapeutics, and Future Directions

Julie A. Nelson[1] · **Kelly G. Knupp**[1]

Accepted: 1 June 2023 / Published online: 23 June 2023

Abstract

Lennox-Gastaut syndrome is a severe drug-resistant developmental and epileptic encephalopathy with slow spike and wave on EEG (DEE-SSW) composing about 1–2% of epilepsy patients. Seizures in DEE-SSW are caused by a variety of etiologies, and there is a large unmet treatment need as seizures are usually treatment-resistant and individuals are often unable to function independently. The updated definition by the International League Against Epilepsy has established formal diagnostic criteria allowing for more uniform diagnosis. This article provides a review of typical medication management and treatment strategies, including new and developing surgical approaches. Future directions in treatment include expanding genetic testing with the potential for gene therapy and continuously improving surgical options with the goal to prevent progression to DEE-SSW.

Keywords Lennox-Gastaut syndrome · Developmental and epileptic encephalopathy · Anti-seizure medication · Novel therapeutics · Review

Introduction

Lennox-Gastaut syndrome is a severe drug-resistant developmental and epileptic encephalopathy (DEE-SSW), consisting of numerous underlying etiologies and as such has a large unmet treatment need. About 1–10% of children with epilepsy have transitioned to DEE-SSW, and it represents around 1–2% of all epilepsy patients [1]. This epilepsy syndrome was first described in 1966 by Gastaut as a severe type of childhood epilepsy, intractable to treatment, and characterized by frequent tonic seizures, atypical absence seizures, intellectual disability, and slow spike-and-wave discharges [2]. He termed the syndrome "childhood epileptic encephalopathy with diffuse slow spike-waves" or "Lennox syndrome" [2]. The ILAE first recognized this syndrome in 1989, further describing the condition, though has only recently established formal diagnostic criteria [3, 4]. The goal of this review is to provide an update regarding the new diagnostic criteria and new and developing treatments of this syndrome.

✉ Julie A. Nelson
Julie.nelson@childrenscolorado.org

[1] Section of Child Neurology, Children's Hospital Colorado, Anschutz School of Medicine, University of Colorado, Aurora, CO, USA

Definition

The ILAE has recently published updated criteria to define DEE-SSW as a syndrome characterized by (1) multiple types of drug-resistant seizures with onset prior to 18 years (one of which must include tonic seizures); (2) cognitive and potentially behavioral impairments, not necessarily present at seizure onset; and (3) diffuse slow spike-and-wave (SSW) and generalized paroxysmal fast activity (PFA) on EEG [3]. There has been evolution in the definition for DEE-SSW compared to the prior definition from the ILAE in 1989, in which DEE-SSW was described as an epilepsy manifesting in children from ages 1–8 years with the most common seizure types reported as tonic-axial, atonic, and absence seizures, though other types such as myoclonic, GTC, or focal seizures were also described [4]. Tonic seizures were not considered mandatory. EEG criteria are now more specific, with the prior definition described as usually having slow spike and wave (< 3 Hz), now updated to ≤ 2.5 Hz in the 2022 definition. In addition, the EEG was previously described as having bursts of fast rhythms nearing 10 Hz and is now defined as diffuse or bilateral fast activity (≥ 10 Hz)

in sleep. Both SSW and PFA are now requirements in the current definition, while SSW was mentioned as a usual characteristic in the prior definition. In addition, the prior definition reported that there was intellectual disability (previously defined as mental retardation) and mostly unfavorable development, though this was not a clear criterion. The updated definition has also expanded to include individuals with seizure onset prior to 18 years of age, allowing more individuals to meet diagnostic criteria, rather than the prior definition's description of seizure onset between 1 and 8 years of age [3, 4].

Existing ASMs and Current Treatment Strategies

There are currently seven anti-seizure medications (ASMs) with an FDA approval to treat DEE-SSW as adjunctive treatment: felbamate, lamotrigine, topiramate, rufinamide, clobazam, and the more newly approved ASMs fenfluramine and cannabidiol.

The American Academy of Neurology (AAN), in conjunction with the American Epilepsy Society, previously reported that felbamate is effective for adjunctive treatment in DEE-SSW in 1999, though caution was needed regarding its use given the possible side effects of aplastic anemia and liver failure [5]. In an updated practice guideline in 2004, the group reported that lamotrigine and topiramate were found to be effective in treating drop attacks in DEE-SSW based on level A evidence [6]. It has most recently revised its recommendations for treatment-resistant epilepsy in 2018, with the recommendation that rufinamide was an effective add-on treatment for DEE-SSW based on 2 class 1 studies [7, 8] with level A evidence [9]. It also reports that clobazam is probably effective as add-on therapy for DEE-SSW based on 2 class II studies [10, 11] with level B evidence [9].

Both clobazam and rufinamide have been found to be protective against additional seizure types in addition to motor seizures associated with a drop. The trials for clobazam did find that at the high (1 mg/kg/day) dose, there was a significant reduction in both drop and non-drop seizures [10, 11]. Rufinamide was found to significantly reduce all seizure types ($p=0.0015$), have a greater reduction in absence and atypical absence seizures ($p=0.0222$), reduce atonic seizures ($p=0.0125$) in a double-blind, randomized, placebo-controlled trial in patients with DEE-SSW [7]. In addition, rufinamide was found to significantly reduce the frequency of tonic seizures ($p=0.031$), myoclonic seizures ($p=0.021$), and partial seizures ($p=0.025$) compared with placebo in another multi-center placebo-controlled trial [8].

Anti-seizure medications (ASMs) which may also be commonly used may include valproate, levetiracetam, zonisamide, ethosuximide, perampanel, and brivaracetam, though they do not currently have an FDA approval [12, 13]. In fact, recent clinical trials for DEE-SSW found levetiracetam, valproate, topiramate, clobazam, lamotrigine, and rufinamide [14, 15] as the most frequent concomitant medications for enrolled patients reflecting real-world evidence for use of these ASMs.

According to the DEE-SSW Transition of Care advisory board meeting in 2017, ASMs recommended for the treatment of DEE-SSW were divided into tiers. Tier 1 included the FDA approved ASMs for DEE-SSW, included clobazam, lamotrigine, rufinamide, topiramate, and cannabidiol [12]. Tier 2 was composed of ASMs commonly used, including levetiracetam, perampanel, and zonisamide. Tier 3 represents the ASMs which are less frequently used in DEE-SSW treatment and with limited data to support efficacy or potential for side effects, including felbamate, lacosamide, brivaracetam, and cenobamate [12].

An expert panel on management of DEE-SSW in 2017 reports that upon new diagnosis of DEE-SSW, the first ASM should be valproate [13]. If seizures persist, lamotrigine should be added. If seizures are still occurring, then rufinamide should be added, followed by attempts to wean the valproate or the lamotrigine as there is no evidence of the effectiveness of more than 2 ASMs in combination, other than unnecessarily exposing the patient to possible side effects [13] (Table 1).

Epidiolex, a highly purified form of cannabidiol, was FDA approved for treatment of DEE-SSW in 2018 after the results of two double-blind, placebo-controlled trials [14, 15]. In the first study, 225 patients aged 2–55 years with DEE-SSW with 2 or more drop seizures (defined as seizures associated with a fall) per week were given doses of 20 mg/kg/day, 10 mg/kg/day, and placebo. After 14 weeks of treatment, the 20 mg/kg/day group had a 41.9% reduction in drop seizures ($p=0.005$ compared to placebo), 10 mg/kg/day group had a 37.2% reduction ($p=0.002$ compared to placebo), and placebo had 17.2% [14]. The median percent reduction of frequency of all seizures was 38.4% in the 20 mg/kg/day cannabidiol group ($p=0.009$), 36.4% in the 10-mg cannabidiol group ($p=0.002$), and 18.5% in the placebo group. Fourteen patients developed elevated liver aminotransferase concentrations [14]. In the second phase III trial, 171 patients with the same seizure frequency criteria experienced a median percentage reduction in drop seizure frequency of 43.9% in the 20 mg/kg/day group compared to 21.8% in the placebo group ($p=0.0135$). The most common side effects were diarrhea, decreased appetite, somnolence, vomiting, and pyrexia [15].

Fenfluramine was recently approved in 2022 for treatment of DEE-SSW after approval for treatment of Dravet syndrome in 2020 based on two clinical trials [16, 17]. The multi-center, double-blind, placebo-controlled, parallel group phase 3 trial for DEE-SSW consisted of 263 patients [18]. Patients must have experienced 2 or more seizures associated with a fall (termed "drop seizures" in the

Table 1 Anti-seizure medications

ASM	FDA approval for DEE-SSW	Common adverse reactions	Contra-indications	Lab monitoring	Special considerations	Notable interactions
Brivaracetam	No	Psychiatric disturbance Sedation Dizziness	Hypersensitivity to brivaracetam or component of formulation	Baseline CBC with differential Liver function Renal function Assessment for depression and suicidality	Consider if LEV was effective but had to discontinue due to behavioral side effects	None
Cenobamate	No	Maculopapular rash DRESS (drug reaction with eosinophilia and systemic symptoms) Shortened QTc interval Fatigue Dizziness	Familial short QT syndrome Hypersensitivity to cenobamate or component of formulation	Liver function Potassium as indicated Assessment for depression and suicidality	None	Caution with additional sodium channel blockers due to additive side effects and arrhythmia risk Moderately inhibits CYP2C19 (clobazam levels increased)
Clobazam	Yes	Drowsiness Drooling Aggressive behavior Irritability	Hypersensitivity to clobazam or component of formulation	CBC Liver function Renal function Assessment for depression and suicidality	Metabolized by CYP2C19 and CYP3A4	Levels may be increased with concomitant epidiolex, felbamate, cenobamate
Epidiolex	Yes	Weight loss Decreased appetite Diarrhea Vomiting	Hypersensitivity to epidiolex or component of formulation	Liver function testing at baseline, 1 month, 3 months, 6 months of initiation. Baseline CBC Assessment for depression/suicidality	Risk of transaminitis Inhibits CYP2C19	May increase clobazam levels
Felbamate	Yes	Drowsiness Weight loss	Hypersensitivity to felbamate, carbamates, history of blood dyscrasia or hepatic dysfunction	CBC with diff Reticulocyte count Liver function At baseline then every 2 weeks for the first month, once monthly for 3 months, then can gradually decrease frequency	Black box warning for aplastic anemia and liver failure Inhibits 2C19 (weak)	May increase clobazam levels
Fenfluramine	Yes	Elevated blood pressure Pulmonary hypertension Serotonin syndrome Valvular heart disease Weight loss CNS depression	Hypersensitivity to fenfluramine or component of formulation Concomitant use within 14 days of a monoamine oxidase inhibitor	None	REMs program, baseline echocardiogram and every 6 months required	Clobazam may increase levels; limit dose when used in conjunction with stiripentol and clobazam
Lamotrigine	Yes	Aseptic meningitis Blood dyscrasias Hypersensitivity reactions	Hypersensitivity to lamotrigine or component of formulation	EKG in patients with known cardiac disease or major risk factors Consider CBC and renal and hepatic function testing	Slow initial titration due to Stevens Johnson risk	Valproate inhibits metabolism, decrease dose by ½ when adding concomitant VPA

Table 1 (continued)

ASM	FDA approval for DEE-SSW	Common adverse reactions	Contra-indications	Lab monitoring	Special considerations	Notable interactions
Levetiracetam	No	Behavioral problems and psychotic symptoms Drowsiness Delayed Hypersensitivity reactions Elevated blood pressure	Hypersensitivity to levetiracetam or component of formulation	Psychiatric and behavioral disturbance Renal function CBC Diastolic blood pressure in children < 4 years	None	None
Perampanel	No	Dizziness Aggression Vertigo Drowsiness	Hypersensitivity to perampanel or component of formulation	Renal function Hepatic function Assess for psychiatric disturbance	Boxed warning for worsening of aggression, anger, homicidal ideation, within the first 6 weeks with or without prior psychiatric history	None
Rufinamide	Yes	Shortened QT interval Nausea Dizziness Drowsiness Headache	Familial short QT syndrome Hypersensitivity to rufinamide or component of formulation	CBC Signs and symptoms of suicidality Consider EKG with concurrent medications which can shorten QT interval	None	None
Topiramate	Yes	Cognitive dysfunction Metabolic acidosis Nephrolithiasis Ocular effects Oligohidrosis Weight loss	Hypersensitivity to topiramate or component of formulation	Electrolytes Ammonia in patients with unexplained lethargy Intraocular pressure Kidney stones	None	None
Valproate	No	Alopecia Abdominal pain Thrombocytopenia Dizziness	Hypersensitivity to valproate or component of formulation Hepatic disease or impairment Urea cycle disorders Blood dyscrasias	Liver enzymes Ammonia with mental status change CBC Lipase with persistent vomiting	Avoid use in women of childbearing age if possible	Inhibits metabolism of lamotrigine
Zonisamide	No	Anorexia Dizziness Drowsiness	Hypersensitivity to zonisamide, sulfonamides, or component of formulation	Electrolytes Ammonia in patients with unexplained lethargy	None	

study) per week during a baseline period and were treated for 12 weeks with a 2-week dose titration with groups randomized to placebo, 0.7 mg/kg/day dose, or 0.2 mg/kg/day. Patients in the 0.7 mg/kg/day group achieved a 19.9 percentage point drop in seizures ($p = 0.001$) compared to placebo, the primary endpoint. Patients in the 0.2 mg/kg/day group experienced a 10.5 percentage point reduction in seizures ($p = 0.09$). Generalized tonic clonic seizures (GTC) were the seizure type most reduced with fenfluramine treatment, with a 45.7% reduction in the 0.7 mg/kg/day group ($p = 0.001$) and a 58.2% reduction in the 0.2 mg/kg/day group ($p < 0.001$) [18].

Perampanel had been studied in a small case study ($n = 13$) of DEE-SSW patients treated with adjunctive therapy, and at a 10-month follow-up, 69% were found to have a $\geq 50\%$ reduction in total seizure frequency [19]. In addition, it had briefly been studied as a potential adjunctive therapy, though the trial was discontinued due to lack of recruitment [20].

Novel Therapeutics

There are several new anti-seizure medications that are currently undergoing clinical trials. While there may be further treatment options for the DEE-SSW patient population, this is further evidence of the unmet treatment need.

There was a recent case series in 2022 describing four patients with DEE-SSW who were treated with the newer anti-seizure medication cenobamate, which was FDA-approved for focal seizures in 2019 [21]. Focal seizures may be a predominant seizure type in some patients with DEE-SSW. The case series followed 4 patients with DEE-SSW who are treated with cenobamate, a drug with a novel mechanism consisting of inhibiting persistent currents of voltage-gated sodium channels and acting as a positive allosteric modulator of $GABA_A$ receptor-binding sites. Four adults with a diagnosis of DEE-SSW and history of focal seizures and drug resistance were included, and after treatment with cenobamate for 12 months, they experienced between a 25 and 74% reduction in seizures, two of which experienced a greater than 50% reduction in seizures [21].

The drug soticlestat is a promising first-in-class selective inhibitor of cholesterol 24-hydroxylase (CH24H). CH24H functions to catalyze the conversion from cholesterol to 24S-hydroxycholesterol and is mainly expressed in neurons [22]. 24S-hydroxycholesterol is thought to be toxic, leading to oxidative stress and inflammation. In animal models, soticlestat has been shown to decrease glutamate levels and lead to reduced hyperexcitability [22]. A phase 2, randomized, double-bind, placebo-controlled study evaluated soticlestat in children 2–17 years with either Dravet syndrome (DS) or DEE-SSW [23]. Children with DEE-SSW were required to have at least 4 or more seizures associated with a fall (drop seizure) per month to enroll. One hundred and thirty-nine children were recruited into study (51 DS, 88 DEE-SSW). After an 8-week dose titration period and 12-week maintenance period, median reductions in convulsive and drop seizures approached significance 17.08% ($p = 0.116$) in children with DEE-SSW. The most common side effects were lethargy and constipation [23]. As the phase 2 trial was potentially underpowered in DEE-SSW patients, soticlestat is currently undergoing a phase 3 international, double-blind, placebo-controlled phase 3 trial in DEE-SSW with results expected in 2023/2024.

Carisbamate is currently being studied for treatment of DEE-SSW, and in the recruitment stage of a phase 3 clinical trial. This medication has been shown to inhibit voltage-gated sodium channels expressed in rat hippocampal neurons [24] in addition to reducing pre-synaptic glutamate levels in rat dentate gyrus [25]. This drug had previously been trialed in patients over 16 years of age with intractable focal epilepsy though results were of mixed significance [26–28]. Carisbamate is currently undergoing in a phase I trial in children and adults with DEE-SSW [29].

Lorcaserin is a novel therapeutic drug with a similar mechanism of action to fenfluramine, working as a selective serotonin receptor (5-HT2C) agonist for receptors located in the central nervous system. It has been shown to decrease the frequency of non-convulsive seizures in a rat model [30]. There is a retrospective case series without a control group in a small multi-center cohort of children and young adults with drug-resistant focal epilepsy ($n = 3$), intractable generalized epilepsies ($n = 3$) including Dravet syndrome ($n = 20$) and DEE-SSW ($n = 9$) [31]. Lorcaserin was associated with a reduction of motor seizures in all groups: 50% in DEE-SSW, 43% in Dravet syndrome, and 23% in drug-resistant/generalized epilepsies. Major side effects (reported by > 10 patients) were decreased appetite, decreased attentiveness, and weight loss [31]. It is currently in phase 3 clinical trials for Dravet syndrome.

Surgical Approaches

In addition to anti-seizure medications, there are also promising surgical approaches to offer other than the existing treatments of VNS and corpus callosotomy. Deep brain simulation (DBS) of the anterior nucleus of the thalamus for treatment of focal onset seizures was approved in 2018 after the results of the SANTE trial [32]. However, there is a growing body of evidence that chronic stimulation of the centromedian (CM) nucleus of the thalamus may be efficacious in reducing seizures in DEE-SSW. The CM represents a main source of input to the striatum, in addition to having connections to the brainstem and cortex, and plays a role in attention, arousal, and coordination [33]. In addition, the

centromedian parafascicular nucleus has been shown to be involved early on the generation of generalized spike wave discharges, preceding involvement of anterior nucleus of the thalamus, which is thought to have a role in propagation of generalized-onset seizures [34]. Given that the centromedian parafascicular nucleus has projections to the bilateral frontocentral cortices, the area of maximal prominence where generalized discharges are noted on scalp EEG, and is activated early on in generalized spike wave discharges, this nucleus is thought to either drive, or have an important early role, in the propagation of generalized onset seizures [34].

A case series from 2006 evaluated 13 patients with DEE-SSW from 4 to 22 years of age who underwent bilateral CM implantation and found that overall seizure reduction was 80% at 18 months of follow-up [35].

The ESTEL trial, a prospective, double-blind, randomized trial of deep brain stimulation (DBS) in the bilateral centromedian (CM) nuclei of the thalamus in patients with DEE-SSW was recently completed [36]. From years 2017–2019, 19 young adults with DEE-SSW underwent implantation of DBS device to bilateral CM nuclei, 10 in the treatment and 9 in the control group.

Three months after implantation, half of patients received 3 months of stimulation as part of the blinded phase, and then all received 3 months of stimulation. The DBS stimulation settings were slightly slower than the SANTE trial (goal voltage of 2.5 V, while SANTE trial voltage began at 5 V and could increase to 7.5 V). The remaining parameters of pulse width of 90 µs, 145 Hz frequency (though in SANTE could increase to 185 Hz), and cycling "on" at 1 min and "off" at 5 min were the same as the SANTE trial [32]. The primary outcome was the proportion of participants with $\geq 50\%$ reduction in diary-recorded seizures in the last month of the blinded period, which was achieved by 50% of the stimulation group ($n=5$) compared with 22% ($n=2$) of controls ($p=0.25$). The secondary outcome was the proportion of patients with a $\geq 50\%$ reduction in electrographic seizures on 24-h ambulatory EEG recording done at the end of the third month of the blinded period, which was 89% ($n=8$) in the stimulation group compared with none of the controls ($p=0.05$). In addition, after all patients entered the treatment group, subjective reports from parents/caregivers of increased alertness occurred in 95% (18/19) and feelings overall benefit were reported by 79% (15/19) [36]. This study was only powered to find a large difference (at least 70% seizure reduction with stimulation) and given the relatively low number of subjects ($n=19$), it is possible that a repeat study with larger numbers of patients, there may be statistically significant results [36].

While limited, there is growing evidence for the use of responsive neurostimulation (RNS) in DEE-SSW with promising results. One case series describes two patients with clear benefit from RNS implanted into the bilateral centromedian nuclei, with a 70−95% seizure reduction 8–12 months after implantation [37].

There is currently a phase II study in recruitment to evaluate RNS in DEE-SSW patients with the plan to implant two neurostimulators with depth leads in the bilateral CM in addition to cortical or strip leads targeting the prefrontal cortex [38].

Future Directions

In addition to newly developing ASMs and expanding surgical options, the importance of continuing the pursuit of identifying the underlying etiology for the patient's epilepsy cannot be understated. With the continued development and widespread use of genetic testing such as whole exome and whole genome sequencing, there may be more targeted treatments in the future, such as gene therapy [39].

In summary, there are promising new treatments of DEE-SSW in both pharmacologic realm and with the advancement of neurostimulation, including both DBS and RNS devices. As future developments in novel therapeutics and surgical techniques may lead to the increasing use of tailored treatments for a patient's epilepsy, the progression to DEE-SSW may be able to be avoided in some patients. However, the underlying heterogeneity and poorly understood pathophysiology of DEE-SSW do remain significant challenges, and more research is needed in this area.

Declarations

Conflict of Interest None.

References

1. Lennox Gastaut Syndrome. Available at: https://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=GB&Expert=2382
2. Gastaut H, Roger J, Soulayrol R, Tassinari CA, Régis H, Dravet C, Bernard R, Pinsard N, Saint-Jean M. Childhood epileptic encephalopathy with diffuse slow spike-waves (otherwise known as "petit mal variant") or Lennox syndrome. Epilepsia. 1966;7(2):139–79. https://doi.org/10.1111/j.1528-1167.1966.tb06263.x. PMID: 4959714.
3. Specchio N, Wirrell EC, Scheffer IE, Nabbout R, Riney K, Samia P, Guerreiro M, Gwer S, Zuberi SM, Wilmshurst JM, Yozawitz E, Pressler R, Hirsch E, Wiebe S, Cross HJ, Perucca E, Moshé SL, Tinuper P, Auvin S. 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(6):1398–442. https://doi.org/10.1111/epi.17241. Epub 2022 May 3 PMID: 35503717.
4. Proposal for revised classification of epilepsies and epileptic syndromes. Commission on Classification and Terminology of the International League Against Epilepsy. Epilepsia. 1989 Jul-Aug;30(4):389–99. https://doi.org/10.1111/j.1528-1157.1989.tb05316.x. PMID: 2502382.

5. French J, Smith M, Faught E, Brown L. Practice advisory: the use of felbamate in the treatment of patients with intractable epilepsy: report of the Quality Standards Subcommittee of the American Academy of Neurology and the American Epilepsy Society. Neurology. 1999;52(8):1540–5. https://doi.org/10.1212/wnl.52.8.1540. PMID: 10331676.
6. French JA, Kanner AM, Bautista J, Abou-Khalil B, Browne T, Harden CL, Theodore WH, Bazil C, Stern J, Schachter SC, Bergen D, Hirtz D, Montouris GD, Nespeca M, Gidal B, Marks WJ Jr, Turk WR, Fischer JH, Bourgeois B, Wilner A, Faught RE Jr, Sachdeo RC, Beydoun A, Glauser TA; Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology; Quality Standards Subcommittee of the American Academy of Neurology; American Epilepsy Society. Efficacy and tolerability of the new antiepileptic drugs II: treatment of refractory epilepsy: report of the Therapeutics and Technology Assessment Subcommittee and Quality Standards Subcommittee of the American Academy of Neurology and the American Epilepsy Society. Neurology. 2004 Apr 27;62(8):1261–73. https://doi.org/10.1212/01.wnl.0000123695.22623.32. PMID: 15111660.
7. Glauser T, Kluger G, Sachdeo R, Krauss G, Perdomo C, Arroyo S. Rufinamide for generalized seizures associated with Lennox-Gastaut syndrome. Neurology. 2008;70(21):1950–8. https://doi.org/10.1212/01.wnl.0000303813.95800.0d. Epub 2008 Apr 9 PMID: 18401024.
8. Ohtsuka Y, Yoshinaga H, Shirasaka Y, Takayama R, Takano H, Iyoda K. Rufinamide as an adjunctive therapy for Lennox-Gastaut syndrome: a randomized double-blind placebo-controlled trial in Japan. Epilepsy Res. 2014;108(9):1627–36. https://doi.org/10.1016/j.eplepsyres.2014.08.019. Epub 2014 Sep 2 PMID: 25219353.
9. Kanner AM, Ashman E, Gloss D, Harden C, Bourgeois B, Bautista JF, Abou-Khalil B, Burakgazi-Dalkilic E, Llanas Park E, Stern J, Hirtz D, Nespeca M, Gidal B, Faught E, French J. Practice guideline update summary: efficacy and tolerability of the new antiepileptic drugs II: treatment-resistant epilepsy: report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology and the American Epilepsy Society. Neurology. 2018 Jul 10;91(2):82–90. doi: https://doi.org/10.1212/WNL.0000000000005756. Epub 2018 Jun 13. Erratum in: Neurology. 2018 Dec 11;91(24):1117. PMID: 29898974.
10. Conry JA, Ng YT, Paolicchi JM, Kernitsky L, Mitchell WG, Ritter FJ, Collins SD, Tracy K, Kormany WN, Abdulnabi R, Riley B, Stolle J. Clobazam in the treatment of Lennox-Gastaut syndrome. Epilepsia. 2009;50(5):1158–66. https://doi.org/10.1111/j.1528-1167.2008.01935.x. Epub 2008 Dec 15 PMID: 19170737.
11. Ng YT, Conry JA, Drummond R, Stolle J, Weinberg MA; OV-1012 Study Investigators. Randomized, phase III study results of clobazam in Lennox-Gastaut syndrome. Neurology. 2011 Oct 11;77(15):1473–81. https://doi.org/10.1212/WNL.0b013e318232de76. Epub 2011 Sep 28. PMID: 21956725.
12. Montouris G, Aboumatar S, Burdette D, Kothare S, Kuzniecky R, Rosenfeld W, Chung S. Expert opinion: Proposed diagnostic and treatment algorithms for Lennox-Gastaut syndrome in adult patients. Epilepsy Behav. 2020 Sep;110:107146. https://doi.org/10.1016/j.yebeh.2020.107146. Epub 2020 Jun 18. PMID: 32563898.
13. 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;29(8):505. https://doi.org/10.3389/fneur.2017.00505. PMID:29085326;PMCID:PMC5649136.
14. Devinsky O, Patel AD, Cross JH, Villanueva V, Wirrell EC, Privitera M, Greenwood SM, Roberts C, Checketts D, VanLandingham KE, Zuberi SM; GWPCARE3 Study Group. Effect of cannabidiol on drop seizures in the Lennox-Gastaut syndrome. N Engl J Med. 2018 May 17;378(20):1888–1897. https://doi.org/10.1056/NEJMoa1714631. PMID: 29768152.
15. Thiele EA, Marsh ED, French JA, Mazurkiewicz-Beldzinska M, Benbadis SR, Joshi C, Lyons PD, Taylor A, Roberts C, Sommerville K; GWPCARE4 Study Group. Cannabidiol in patients with seizures associated with Lennox-Gastaut syndrome (GWPCARE4): a randomised, double-blind, placebo-controlled phase 3 trial. Lancet. 2018 Mar 17;391(10125):1085–1096. https://doi.org/10.1016/S0140-6736(18)30136-3. Epub 2018 Jan 26. PMID: 29395273.
16. Lagae L, Sullivan J, Knupp K, Laux L, Polster T, Nikanorova M, Devinsky O, Cross JH, Guerrini R, Talwar D, Miller I, Farfel G, Galer BS, Gammaitoni A, Mistry A, Morrison G, Lock M, Agarwal A, Lai WW, Ceulemans B; FAiRE DS Study Group. Fenfluramine hydrochloride for the treatment of seizures in Dravet syndrome: a randomised, double-blind, placebo-controlled trial. Lancet. 2019 Dec 21;394(10216):2243–2254. https://doi.org/10.1016/S0140-6736(19)32500-0. Epub 2019 Dec 17. PMID: 31862249.
17. Nabbout R, Mistry A, Zuberi S, Villeneuve N, Gil-Nagel A, Sanchez-Carpintero R, Stephani U, Laux L, Wirrell E, Knupp K, Chiron C, Farfel G, Galer BS, Morrison G, Lock M, Agarwal A, Auvin S; FAiRE, DS Study Group. Fenfluramine for treatment-resistant seizures in patients with Dravet syndrome receiving stiripentol-inclusive regimens: a randomized clinical trial. JAMA Neurol. 2020 Mar 1;77(3):300–308. https://doi.org/10.1001/jamaneurol.2019.4113. PMID: 31790543; PMCID: PMC6902175.
18. Knupp KG, Scheffer IE, Ceulemans B, Sullivan JE, Nickels KC, Lagae L, Guerrini R, Zuberi SM, Nabbout R, Riney K, Shore S, Agarwal A, Lock M, Farfel GM, Galer BS, Gammaitoni AR, Davis R, Gil-Nagel A. Efficacy and safety of fenfluramine for the treatment of seizures associated with Lennox-Gastaut syndrome: a randomized clinical trial. JAMA Neurol. 2022;79(6):554–64. https://doi.org/10.1001/jamaneurol.2022.0829. PMID:35499850;PMCID:PMC9062770.
19. 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. https://doi.org/10.1016/j.yebeh.2017.05.036. Epub 2017 Jul 14 PMID: 28715780.
20. Study of perampanel as adjunctive treatment for inadequately controlled seizures associated with Lennox-Gastaut syndrome. https://clinicaltrials.gov/ct2/show/results/NCT02834793?term=perampanel&cond=Lennox+Gastaut+Syndrome&draw=2&rank=1
21. 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(1):129. https://doi.org/10.3390/jcm12010129. PMID:36614931;PMCID:PMC9821211.
22. Nishi T, Kondo S, Miyamoto M, Watanabe S, Hasegawa S, Kondo S, Yano J, Watanabe E, Ishi T, Yoshikawa M, Ando HK, Farnaby W, Fujimoto S, Sunahara E, Ohori M, During MJ, Kuroita T, Koike T. Soticlestat, a novel cholesterol 24-hydroxylase inhibitor shows a therapeutic potential for neural hyperexcitation in mice. Sci Rep. 2020;10(1):17081. https://doi.org/10.1038/s41598-020-74036-6. PMID:33051477;PMCID:PMC7553946.
23. Hahn CD, Jiang Y, Villanueva V, Zolnowska M, Arkilo D, Hsiao S, Asgharnejad M, Dlugos D. 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 Oct;63(10):2671–2683. https://doi.org/10.1111/epi.17367. Epub 2022 Aug 4. PMID: 35841234; PMCID: PMC9804149.
24. Liu Y, Yohrling GJ, Wang Y, Hutchinson TL, Brenneman DE, Flores CM, Zhao B. Carisbamate, a novel neuromodulator, inhibits its voltage-gated sodium channels and action potential firing of

rat hippocampal neurons. Epilepsy Res. 2009;83(1):66–72. https://doi.org/10.1016/j.eplepsyres.2008.09.006. Epub 2008 Nov 14 PMID: 19013768.
25. Lee CY, Lee ML, Shih CC, Liou HH. Carisbamate (RWJ-333369) inhibits glutamate transmission in the granule cell of the dentate gyrus. Neuropharmacology. 2011;61(8):1239–47. https://doi.org/10.1016/j.neuropharm.2011.07.022. Epub 2011 Jul 30 PMID: 21824485.
26. Faught E, Holmes GL, Rosenfeld WE, Novak G, Neto W, Greenspan A, Schmitt J, Yuen E, Reines S, Haas M. Randomized, controlled, dose-ranging trial of carisbamate for partial-onset seizures. Neurology. 2008;71(20):1586–93. https://doi.org/10.1212/01.wnl.0000334751.89859.7f. PMID: 19001248.
27. Halford JJ, Ben-Menachem E, Kwan P, Ness S, Schmitt J, Eerdekens M, Novak G. A randomized, double-blind, placebo-controlled study of the efficacy, safety, and tolerability of adjunctive carisbamate treatment in patients with partial-onset seizures. Epilepsia. 2011;52(4):816–25. https://doi.org/10.1111/j.1528-1167.2010.02960.x. Epub 2011 Feb 14 PMID: 21320109.
28. Sperling MR, Greenspan A, Cramer JA, Kwan P, Kälviäinen R, Halford JJ, Schmitt J, Yuen E, Cook T, Haas M, Novak G. Carisbamate as adjunctive treatment of partial onset seizures in adults in two randomized, placebo-controlled trials. Epilepsia. 2010;51(3):333–43. https://doi.org/10.1111/j.1528-1167.2009.02318.x. Epub 2009 Oct 27 PMID: 19863578.
29. Carisbamate in adult & pediatric subjects with Lennox-Gastaut syndrome. https://clinicaltrials.gov/ct2/show/NCT04062981?term=lennox+gastaut&cond=carisbamate&draw=2&rank=1.
30. Venzi M, David F, Bellet J, Cavaccini A, Bombardi C, Crunelli V, Di Giovanni G. Role for serotonin2A (5-HT2A) and 2C (5-HT2C) receptors in experimental absence seizures. Neuropharmacology. 2016 Sep;108:292–304. https://doi.org/10.1016/j.neuropharm.2016.04.016. Epub 2016 Apr 13. PMID: 27085605; PMCID: PMC4920646.
31. Tolete P, Knupp K, Karlovich M, DeCarlo E, Bluvstein J, Conway E, Friedman D, Dugan P, Devinsky O. Lorcaserin therapy for severe epilepsy of childhood onset: a case series. Neurology. 2018 Oct 30;91(18):837–839. doi: https://doi.org/10.1212/WNL.0000000000006432. Epub 2018 Sep 26. PMID: 30258026; PMCID: PMC6207415.
32. Fisher R, Salanova V, Witt T, Worth R, Henry T, Gross R, Oommen K, Osorio I, Nazzaro J, Labar D, Kaplitt M, Sperling M, Sandok E, Neal J, Handforth A, Stern J, DeSalles A, Chung S, Shetter A, Bergen D, Bakay R, Henderson J, French J, Baltuch G, Rosenfeld W, Youkilis A, Marks W, Garcia P, Barbaro N, Fountain N, Bazil C, Goodman R, McKhann G, Babu Krishnamurthy K, Papavassiliou S, Epstein C, Pollard J, Tonder L, Grebin J, Coffey R, Graves N; SANTE Study Group. Electrical stimulation of the anterior nucleus of thalamus for treatment of refractory epilepsy. Epilepsia. 2010 May;51(5):899–908. https://doi.org/10.1111/j.1528-1167.2010.02536.x. Epub 2010 Mar 17. PMID: 20331461.
33. Ilyas A, Pizarro D, Romeo AK, Riley KO, Pati S. The centromedian nucleus: anatomy, physiology, and clinical implications. J Clin Neurosci. 2019;63:1–7. https://doi.org/10.1016/j.jocn.2019.01.050. Epub 2019 Feb 28 PMID: 30827880.
34. Tyvaert L, Chassagnon S, Sadikot A, LeVan P, Dubeau F, Gotman J. Thalamic nuclei activity in idiopathic generalized epilepsy: an EEG-fMRI study. Neurology. 2009;73(23):2018–22. https://doi.org/10.1212/WNL.0b013e3181c55d02. PMID: 19996076.
35. Velasco AL, Velasco F, Jiménez F, Velasco M, Castro G, Carrillo-Ruiz JD, Fanghänel G, Boleaga B. Neuromodulation of the centromedian thalamic nuclei in the treatment of generalized seizures and the improvement of the quality of life in patients with Lennox-Gastaut syndrome. Epilepsia. 2006;47(7):1203–12. https://doi.org/10.1111/j.1528-1167.2006.00593.x. PMID: 16886984.
36. Dalic LJ, Warren AEL, Bulluss KJ, Thevathasan W, Roten A, Churilov L, Archer JS. DBS of thalamic centromedian nucleus for Lennox-Gastaut syndrome (ESTEL trial). Ann Neurol. 2022 Feb;91(2):253–267. https://doi.org/10.1002/ana.26280. Epub 2021 Dec 28. Erratum in: Ann Neurol. 2022 Apr 12; PMID: 34877694.
37. Kwon CS, Schupper AJ, Fields MC, Marcuse LV, La Vega-Talbott M, Panov F, Ghatan S. Centromedian thalamic responsive neurostimulation for Lennox-Gastaut epilepsy and autism. Ann Clin Transl Neurol. 2020 Oct;7(10):2035–2040. https://doi.org/10.1002/acn3.51173. Epub 2020 Aug 29. PMID: 32860345; PMCID: PMC7545608.
38. RNS System LGS feasibility study. ClinicalTrials.gov Identifier: NCT05339126. https://clinicaltrials.gov/ct2/show/NCT05339126
39. Zhang L, Wang Y. Gene therapy in epilepsy. Biomed Pharmacother. 2021 Nov;143:112075. https://doi.org/10.1016/j.biopha.2021.112075. Epub 2021 Sep 3. PMID: 34488082.