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Intractable Generalized Epilepsy: Therapeutic Approaches

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Abstract

Purpose of Review To summarize recent developments in therapeutic options, both medical and surgical, for patients with drug-resistant generalized epilepsy syndromes, which continue to be a multifaceted challenge for patients and physicians.

Recent Findings Newer generation pharmaceutical options are now available, such as brivaracetam, rufinamide, lacosamide, perampanel, and cannabidiol. Less restrictive dietary options appear to be nearly as effective as classic ketogenic diet for amelioration of seizures. The latest implantable devices include responsive neurostimulation and deep brain stimulation. Corpus callosotomy is an effective treatment for some seizure types, and newer and less invasive approaches are being explored. Resective surgical options have demonstrated success in carefully selected patients despite generalized electrographic findings on electroencephalogram.

Summary The current literature reflects a widening range of clinical experience with newer anticonvulsant medications including cannabinoids, dietary therapies, surgical approaches, and neurostimulation devices for patients with intractable generalized epilepsy.

Keywords Drug resistant · Refractory · Intractable · Generalized epilepsy

Introduction

Approximately a third of patients suffer from seizure types which are predominantly generalized in nature [1]. Generalized seizures are classified as motor (tonic-clonic, clonic, tonic, myoclonic, myoclonic-tonic-clonic, myoclonic-atonic, atonic, spasms) and non-motor (typical absence, atypical absence, myoclonic absence, absence with eyelid myoclonia) [2•]. Children with intractable epilepsy are at elevated risk for developing adverse social and intellectual outcomes, impaired quality of life, and premature mortality [3]. Earlier recognition of drug-resistant epilepsy (DRE), appropriate syndromic classification, imaging, and genetic testing may offer a clearer understanding of prognosis and potential treatment options.

Genetic Generalized Epilepsies

Primary genetic generalized epilepsies (GGE) constitute 15–20% of all epilepsy syndromes. Overall, approximately 18–36% of patients with GGE continue to have seizures despite two or more trials of appropriately dosed antiepileptic drugs (AEDs), and will fulfill criteria for DRE [4, 5]. Remission rates are sub-syndrome dependent, but febrile seizures, early onset, longstanding epilepsy, multiple seizure types, status epilepticus, developmental delay, and comorbid psychopathology may be other risk factors for intractability [4, 5]. Medication compliance and lifestyle may account for some variability in outcomes or "pseudo-resistance," but it is clear that patients develop DRE even in syndromes classically associated with good prognosis such as childhood absence epilepsy (CAE), juvenile absence epilepsy (JAE), generalized tonic clonic seizures (GTCS) alone, and juvenile myoclonic epilepsy (JME). In retrospective cohorts, 7% of patients with CAE, 11% of patients with JAE, and up to 40% of patients with JME do not ultimately obtain seizure freedom [3].

JME is a common syndrome manifesting around puberty with myoclonus, GTCS, and occasionally absence with a prevalence of 2.8–11.9% of all epilepsies and 26.7% of GGE [6]. The etiology is polygenic, conferring a lifelong propensity toward seizures, though often responsive to proper treatment. However, pharmacoresistance is seen in around 15% of patients and long-term remission in only about 59%. Patients with psychological comorbidities and intellectual difficulty have a higher probability of DRE [4, 6]. Prominent absences or eyelid myoclonia may indicate alternate diagnoses such as JAE or eyelid myoclonia with absences (Jeavon

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syndrome), which are associated with intractability. With regard to EEG characteristics, intermittent 4–6 Hz generalized polyspike and wave discharges are classic, whereas EEG focality and a high abundance of discharges may be concerning findings [4–6].

Generalized Epilepsies Due to Structural, Metabolic, or Unknown Causes

In patients with greater functional and intellectual disability due to causes such as genetic, metabolic, remote infectious, or structural abnormalities, seizures may virtually never remit as is typical for Lennox Gastaut syndrome (LGS) or severe myoclonic epilepsy in infancy (Dravet syndrome). Rates of DRE are also high in patients with other syndromes such as West syndrome, Ohtahara syndrome, the progressive myoclonic epilepsies (PME), myoclonic-atonic epilepsy (Doose syndrome), and other epileptic encephalopathies. Collectively, these syndromes had been referred to as "symptomatic or cryptogenic" generalized epilepsies in the past, and account for about 10% of childhood epilepsy [7]. These patients are at considerable risk for impaired quality of life and early death [7]. Greater details in regard to a few of these syndromes are provided below.

LGS is an epileptic encephalopathy characterized by multiple drug-resistant seizure types (including tonic, atonic, atypical absence, myoclonic, focal seizures, and GTCS), intellectual disability, and an interictal EEG with slow spike-wave complexes and generalized paroxysmal fast activity. The prevalence of LGS is about 2% of all patients with epilepsy, and 4–10% of childhood epilepsies [8]. LGS may be preceded by West syndrome in about a quarter of cases. The etiologies are genetic-structural-metabolic in 70% of patients (such as tuberous sclerosis complex (TSC), malformations of cortical development (MCD), or post-ischemic encephalomalacia), or of unknown cause in the rest. Genetic studies will likely elucidate these cryptogenic cases further, as pathogenic mutations have been recently described involving genes such as ALG13, GABRB3, CHD2, DNM1, SCN8A, STXBP1, FOXG1, among others [8]. DRE, recurrent status epilepticus, and poor neuropsychological outcomes are unfortunately quite prevalent.

Dravet syndrome is a rare epileptic encephalopathy characterized by the onset of prolonged febrile and afebrile seizures in infancy, progressing to DRE with associated cognitive and functional impairments. Myoclonic, GTCS, atypical absence, and focal clonic seizures occur in abundance in early childhood, and frequently persist into adulthood [9]. About 75% of cases are caused by pathogenic mutations in the sodium channel gene SCN1A, but several others have also been implicated [10]. Sodium channel blocking AEDs are thus avoided, as well as vigabatrin.

Doose syndrome is rare and accounts for between 1 and 2% of childhood epilepsies. It begins in children of previously normal development between 1 to 5 years of age, with male predominance [11]. Seizures are predominantly atonic, at times preceded by myoclonus, though absence and GTCS can occur. About a third of affected children will have persistent seizures and experience cognitive declines. Genetic mutations affecting sodium channels or GABA neurotransmission have been found only in a small proportion of patients.

PME is a neurodegenerative syndrome with multiple underlying etiologies, commonly manifested by refractory myoclonus, tonic seizures, and GTCS with progressive neurologic deterioration. Several genetic mutations (including those for Baltic myoclonus, Lafora disease, among others) have been identified offering better characterization and earlier prognostication.

Inborn errors of metabolism may present with a relatively undifferentiated phenotype of generalized seizures and developmental delay. Examples include succinic semialdehyde dehydrogenase deficiency, arginase deficiency, and mitochondrial disorders [10]. Glucose transporter type 1 deficiency syndrome (Glut1DS) is caused by impaired glucose transport across the blood–brain barrier and into astrocytes, attributed to mostly de novo mutations in the SLC2A1 gene. Intractable atypical absences in a young child and hypoglycorrhachia in the presence of low or normal serum lactate levels are diagnostic. Early diagnosis is paramount with good neurodevelopmental and seizure outcomes if the ketogenic diet is initiated [12].

Genetic Testing in Generalized DRE

Precision medicine will eventually require classification of an individual's epilepsy by both clinical syndrome and genetic characterization. Next-generation sequencing has revealed gene mutations associated with epilepsy in up to a third of patients [13]. It is important to highlight that a pathogenic mutation must be correlated with the clinical history and phenotype, due to extreme variability in gene expression. Caution has to be used in interpretation of variants of unknown clinical significance. Practical implications may include early prognostication and choice of medication, for example avoiding certain AEDs in patients with sodium channel mutations. Genetic testing may also have ramifications for surgical outcomes and pursuit.

Antiepileptic Drugs

In drug selection for the treatment of generalized epilepsy, broad-spectrum AEDs should be utilized. Some therapies specific for focal seizures, such as those with primarily sodium channel blocking or GABAergic mechanisms of action (MOA), may provoke certain generalized seizure types [14, 15]. Although a growing number of AEDs are available for use in patients with epilepsy, only valproate, lamotrigine,

levetiracetam, topiramate, and perampanel are currently approved for generalized seizures; with clobazam, felbamate, and rufinamide approved for use specifically in LGS, and vigabatrin and everolimus for use in the treatment of seizures associated with TSC [16, 17•, 18•]. Although not officially proven with Class I data, there is evidence for the use of zonisamide and lacosamide as well [19, 20]. Sodium channel blocking AEDs may occasionally precipitate seizure exacerbation in generalized epilepsy, and are typically avoided. However, carbamazepine, phenytoin, and oxcarbazepine have been utilized in some patients with generalized DRE; despite little data available supporting their use [6, 21]. Brivaracetam and cannabidiol are other recently approved agents available to treat intractable seizures. When choosing among these AEDs to use in a patient with generalized DRE, one must carefully consider the drug's MOA, side effects, and medication interaction profile.

Older Broad-Spectrum Drugs

Valproate and lamotrigine are known as broad-spectrum agents, used for both monotherapy and adjunctive therapy in patients with generalized epilepsy. Several studies have shown valproate to be superior to topiramate and lamotrigine in the treatment of primary generalized seizures [22, 23•]. Since valproate and lamotrigine are often utilized together in a regimen of a patient with generalized DRE, their pharmacokinetic interactions must be kept in mind, with significant inhibition of lamotrigine clearance. Levetiracetam has been shown to have efficacy in the treatment of patients with generalized DRE and can be added to a regimen without fear of pharmacokinetic interaction [24].

Both topiramate and zonisamide are broad-spectrum AEDs with multiple MOA, but only topiramate has been approved for initial monotherapy for generalized epilepsy, with no class I trials for zonisamide. The efficacy of topiramate in the treatment of refractory generalized seizures was evaluated in a randomized control trial (RCT) with significant reduction in seizure rate found those taking topiramate as compared to placebo [25]. In a small retrospective study evaluating the use of zonisamide for generalized DRE, it was shown to be efficacious as well [26]. Medication interactions may occur, but are typically to a relatively lesser extent.

Perampanel

FDA approved in 2015, perampanel works as a noncompetitive AMPA glutamate receptor antagonist with evidence of efficacy against seizures in GGE in addition to focal epilepsy [17•]. It is 95% protein bound and mainly metabolized in the liver with a half-life of 105 h [27]. It does not have significant pharmacokinetic effects on other AEDs, but enzyme inducers may lower perampanel levels. A multicenter, phase 3, placebo-controlled trial found that during a 13-week maintenance period, 31% of patients with GGE and primary GTCS receiving perampanel became seizure-free versus 12% in the placebo group [17•]. The most common side effects were dizziness (32%), fatigue (15%), and irritability (11%), more prevalent at higher dosing. A multicenter retrospective series of patients treated with perampanel for GGE showed a seizure-free rate of 59% overall at 1 year. Seizure frequency was reduced relative to baseline type for GTCS (78%), myoclonic (65%), and absence seizures (48%) [28]. Side effects were reported in a half of patients, mostly mild to moderate.

Lacosamide

Lacosamide was FDA approved in 2009 and enhances the slow inactivation of neuronal sodium channels [27]. Although inactive metabolites are produced in the liver, a high percentage is excreted unchanged. It lacks significant interactions with other AEDs which makes it a candidate for use in the treatment of DRE in the setting of polypharmacy. The most common side effects include dizziness, headache, gastrointestinal upset, and fatigue which are often aggravated when lacosamide is used together with other sodium channel blockers [29].

A 2016 open-label study evaluated the use of lacosamide in patients with GGE [20]. Forty-nine patients 16–65 years of age with diagnoses of JME, CAE, JAE, and other undifferentiated GGEs were included in the study with 39 patients completing the study through maintenance phase. Then, 64% of patients remained seizure-free for at least 6 months and 36% for at least 1 year. A phase 2 trial evaluating the use of lacosamide for the add-on treatment of pediatric patients with syndromes associated with generalized seizures is awaiting publication (NCT:0196851).

Brivaracetam

Brivaracetam was FDA approved in 2016 for the adjunctive treatment of focal seizures. It binds to synaptic vesicle protein 2A which is involved in vesicle exocytosis. Patients with GGE were included in the initial phase 3, double-blind, RCT [30•]. The significantly higher responder rate compared to placebo in this trial, and the chemical similarities of brivaracetam with levetiracetam, suggest that brivaracetam might be useful in treating patients with GGE. Notably, brivaracetam does have a greater risk of drug interactions in comparison to levetiracetam.

Antiepileptic Medications for Lennox Gastaut Syndrome

LGS is associated with a high rate of DRE. Many of the AEDs mentioned above can be used in patients with LGS, but

felbamate, clobazam, and rufinamide are three studied specifically in LGS patients. All three of these medications may have potential interactions with other AEDs.

Felbamate has multiple MOA, but mainly inhibits the NMDA glutamate receptor [31]. It has been used as adjunctive therapy in refractory patients with LGS and as monotherapy in patients with severe DRE. The most serious dangers are aplastic anemia and hepatic failure, both less likely after the first year of treatment [27]. It is a broad-spectrum AED which use is limited in practice by these idiosyncratic adverse reactions. Safer options should be considered first.

Clobazam, a long-acting benzodiazepine approved by the FDA in 2011 for the treatment of seizures associated with LGS, has less fatigue issues and tachyphylaxis compared to other benzodiazepines [32]. A phase 3 placebo-controlled RCT evaluated patients with LGS aged 2–60 years during 12 weeks with clobazam showing a significantly greater reduction in all seizure types as compared to placebo. Long-term follow up from the same investigators showed continued efficacy over time [33]. In Europe, it is approved as a broad-spectrum agent for adjunctive therapy for patients with DRE, not limited to those with an LGS diagnosis [34].

Rufinamide is a sodium channel blocking AED approved by the FDA in 2008 as adjunctive therapy for seizures associated with LGS. Studies, including RCTs, have demonstrated the effectiveness of rufinamide in lowering total seizure frequency, particularly drop attacks, with long-term efficacy and safety [35].

Antiepileptic Medications for Tuberous Sclerosis

Although many of the broad-spectrum AEDs above are used in the treatment of TSC, vigabatrin and everolimus are two agents specifically approved for seizures associated with this condition. Vigabatrin, an irreversible inhibitor of GABA transaminase, increases the accumulation of synaptic GABA. It is not significantly metabolized and has no medication interactions, making it a good choice to use as an adjunct in the treatment of the seizures associated with TSC. Of note, it may worsen absence and myoclonic seizures and should not be used in GGE [14]. Most importantly, in addition to being used as adjunctive therapy in focal epilepsies, it has been shown to have efficacy in the treatment of infantile spasms, especially in patients with TSC [36]. Progressive and permanent bilateral concentric visual field loss is a possible side effect, making it necessary to closely follow visual field testing in treated patients [37].

Everolimus, a mammalian target of rapamycin (mTOR) inhibitor, was approved by the FDA in 2018 for adjunctive treatment of focal seizures associated with TSC. This approval was based on EXIST-3, a double-blind, multicenter RCT showing statistically significant reductions in seizures for patients taking everolimus compared to placebo [18•]. Although only focal seizures were studied, it is possible that this agent may also be effective in the treatment of other seizure types associated with TSC.

Stiripentol

Stiripentol is a GABAergic agent which has been FDA approved as of 2018 to be used as adjunctive therapy with clobazam for the treatment of seizures associated with Dravet Syndrome. The pivotal RCT in patients currently on clobazam and valproate showed that 71% of patients receiving add-on stripentol and 5% of patients receiving placebo had more than a 50% reduction in GTCS [38•]. The efficacy and safety of stripentol in combination with valproate and clobazam started in childhood are maintained long-term into adulthood [9].

Cannabidiol

There has been intense interest recently in the use of cannabis for the treatment of DRE. Nine-delta-tetrahydrocannabinol (THC) and cannabidiol (CBD) are the two most potent cannabinoids in cannabis. CBD, having few psychoactive side effects and an unknown MOA for its anticonvulsant effect, has been the main compound studied. In 2018, the FDA recently approved the pharmaceutical-grade cannabidiol extract, Epidiolex, for the treatment of LGS and Dravet. A recent systematic review showed that CBD is effective in reducing seizure burden in children with drug-resistant LGS and Dravet Syndrome. Evaluating 4 RCTs (LGS or Dravet Syndrome only) and 17 non-randomized studies, the review found that 15 studies (1 RCT and 14 non-randomized studies) reported at least some cases of seizure freedom with administration of a cannabis-based product [39]. The pooled median difference in overall monthly seizure frequency between CBD and placebo in the RCTs was − 19.8% at 14 weeks (95% CI = − 27.0% to − 12.6%; moderate certainty; duration 14 weeks) [39]. In one RCT, 5% of children with Dravet syndrome receiving CBD experienced seizure freedom, whereas none on placebo became seizure-free [40••]. Evaluating three RCTs for monthly differences in GTCS frequency, the pooled median between CBD and placebo was − 26.7% (95% CI = − 38.8% to − 14.8%; moderate certainly; duration 14 weeks). In evaluation of treatment response, one RCT in children with LGS showed that 37% of patients in the CBD group had ≥ 50% reduction in seizure frequency from baseline versus 21% of those on placebo [41••].

Adverse reactions included somnolence, decreased appetite, diarrhea, sleep changes, and transaminitis. CBD has been found to interact with other medications, in particular inhibiting the metabolism of clobazam [39]. Although the data for the use of CBD in LGS and Dravet Syndrome is promising, more research is needed in regard to the efficacy of

cannabidiol for seizures types not associated with these two syndromes.

Dietary Therapies

Ketogenic Diet

In the 1920s, the classic ketogenic diet (KD) first emerged as a nonpharmacological treatment for epilepsy. Although there was a decline in interest due to the serial introduction of anticonvulsants, there was a resurgence in the 1990s when efficacy was reported in a case series of pediatric patients with DRE [42]. In the last two decades, other variants of KD have emerged with evidence to support their use in epilepsy treatment for both pediatric and adult patients.

Classic KD is an extremely regimented high fat, low carbohydrate, and protein diet that induces production of ketone bodies through fat metabolism. It usually consists of a 4:1 ratio of fat to carbohydrates plus protein in grams [43•]. KD is reported to be effective, safe, and well-tolerated as a treatment of pediatric epilepsy patients as young as infants less than 12 months of age, including via formula-based powder [44].

Medium chain triglyceride KD (MCT KD) is a variant on the classic KD. The fat source in MCT KD is medium-chain triglycerides obtained from oils instead of the long-chain triglycerides from standard foods. MCT KD requires less total fat to achieve ketosis and allows more carbohydrate and protein intake. Class III evidence showed that MCT KD has comparable efficacy to classic KD [45].

The MOA underlying the KD remains poorly understood. Many hypotheses have been proposed, including direct antiseizure effects of ketones, regulation of neurotransmitters and ion channels, alteration in cellular bioenergetics and mitochondrial function, reduction in glycolysis, effect of fatty acids, attenuation of neuroinflammation, and modulation of tricarboxylic acid cycle flux [46–48]. Given the complexity of the mediators involved, KD likely exerts its effect through multiple disease-modifying pathways.

KD is considered first line treatment in certain metabolic disorders such as Glut1DS and pyruvate dehydrogenase deficiency. The literature supports the benefit of KD in treatment of pharmacoresistant generalized epilepsies in both children and adults, including LGS, Dravet syndrome, West syndrome, Doose syndrome, and febrile infection-related epileptic syndrome [11, 49–52]. Over the last few years, there has also been increasing use of KD as an adjunct treatment for refractory status epilepticus [53–56].

Patients may require monitoring during initiation, maintenance, and discontinuation of KD. Contraindications to KD include certain inborn errors of metabolism, chronic kidney or liver disease, perpetual noncompliance, and concurrent use of propofol [43•]. Common short-term adverse effects of KD are gastrointestinal disturbances, weight loss, and hyperlipidemia. Potential long-term adverse effects include nephrolithiasis, decreased bone density, liver steatosis, and atherosclerotic effects [57].

Modified Atkins Diet

Modified Atkins diet (MAD) was introduced in 2003 by the John Hopkins Institute, and is typically composed of 10–20 g of carbohydrate per day, which is approximately 1–2:1 ratio of fat to carbohydrates plus protein in grams [43•]. MAD does not require weighing of foods or intensive monitoring as needed for KD. Several studies, including RCTs, have demonstrated the success of MAD in childhood DRE [58]. One RCT and one systematic review and meta-analysis found no significant difference between classical KD and MAD in ≥ 50% and ≥ 90% reduction of seizure frequency at 3 and 6 months in childhood DRE [59, 60]. MAD was specifically reported to reduce seizure frequency in adult patients with generalized DRE [49].

Low Glycemic Index Treatment

Low glycemic index treatment (LGIT) was introduced in 2005 by Harvard investigators, which has a more liberal daily carbohydrate intake of 40–60 g, but only foods with glycemic indices < 50 are allowed [43•]. Maximum efficacy of the less restrictive LGIT is seen at about 12 weeks versus 4 weeks for KD and MAD [46]. Less ketosis is achieved which may prevent its use in metabolic disorders, such as Glut1DS.

Surgical Therapies

Corpus Callosotomy

Corpus callosotomy (CC) has been utilized as a palliative procedure for DRE for more than half a century. Transection is intended to disrupt rapid interhemispheric transcallosal propagation of seizures, particularly from regions of cortex associated with ictal motor manifestations. The target for resection is typically the anterior to mid callosum, with sparing of the posterior fibers in an attempt to mitigate the risks of a sensory disconnection syndrome. However, completion of callosotomy may be performed if amelioration of seizures is unsatisfactory, particularly in younger children or severely intellectually impaired individuals where the risk of causing interruption of interhemispheric perceptual transfer may be lower. Data supports the incremental benefits of completion of CC after anterior transection or with complete callosotomy as initial surgery [61]. Rather than prefrontal interhemispheric disconnection, some have advocated for a more mid to

posterior target for transection in severely intellectually disabled patients with good results. This region may more closely correlate anatomically with the crossing fibers from pre- and primary motor cortex, and targeting there may avoid postoperative complications like akinetic mutism [62].

CC is most efficacious against atonic seizures and GTCS. However, it also appears to be helpful for absence, tonic seizures, and to a lesser extent even myoclonic and focal impaired awareness seizures [61]. Dramatic improvements in seizures have been observed, depending on seizure type, with meaningful improvements in seizures in 88.2% of patients after total CC and 58.6% of patients after anterior CC in a recent meta-analysis [63•]. A long-term outcome study of CC including the use of endoscopic techniques showed 85% of patients with ≥ 50% reduction of seizures resulting in falls, 33% free of such seizures, and overall substantial improvements in GTCS [64]. A prospective longitudinal study showed 56% of patients free of drop attacks, 72% of patients with > 75% reduction in drop attacks, and fewer patients experiencing GTCS at > 5-year follow up [65].

Traditional CC involves a frontal craniotomy, frontal lobar retraction, dissection through the interhemispheric fissure, and transection of the callosum. Specific complications include transitory decreased speech production and gait instability. A typically transient disconnection syndrome may occur in up to 12.5% of patients after total CC, but is less common with anterior CC [63•]. Newer more minimally invasive methods include endoscopic approaches, and more recently magnetic resonance image (MRI)-guided laser interstitial thermal therapy (LITT) [64, 66]. Our recent case series demonstrated the feasibility of LITT CC and proof of concept by pre- and postoperative resting state functional MRI, diffusion tensor imaging, concurrent stereoencephalography (SEEG), and cortical to cortical evoked potentials showing interhemispheric anatomic and functional disruption as intended [66]. Practical anatomic considerations may limit the feasibility of LITT CC which is typically accomplished with 2–3 fibers, where a highly circular callosum may be challenging to ablate.

What initially appear to be widespread or generalized epileptiform EEG abnormalities may become more localized in field after CC, reflecting their true nature as rapidly bisynchronous phenomena [66]. In select patients, for example, those with consistent lateralizing semiological features or hemispheric predominant lesions on neuroimaging, CC may offer to elucidate subsequent focal resective options in addition to palliative improvements in seizure burden.

Vagal Nerve Stimulation

Closed loop vagal nerve stimulation (VNS) has been approved since 1997 in the USA for intractable focal epilepsy, with over 100,000 patients implanted worldwide [67, 68]. The mechanism of action is not well understood, but is thought to derive from vagal excitation affecting the nucleus tractus solitarius which has widespread projections to brainstem, thalamus, and cortex. More recent device updates include responsive stimulation based on seizure-associated heart rate variability. While not initially studied in this population, subsequent retrospective case series and open trial data have demonstrated that VNS is useful for patients with generalized epilepsy syndromes, including GGE, LGS and Dravet [67–70]. Despite lacking FDA approval for this indication, approximately a third of patients have had the device implanted for generalized epilepsy, according to the VNS Therapy Outcome Registry [71].

The effects of VNS on seizures are not usually immediate, but improve with the titration of settings and over time. About 40% of patients respond to VNS by 4 months as defined by a ≥ 50% reduction in seizures, whereas the responder rate nears 60% by 4 years, with 8% of patients reporting seizure freedom [68, 71].

In a recent comparative review of their use in atonic seizures, CC was determined to result in a reduction in seizure burden by half or more in 85.6% of patients, while a responder rate of 57.6% was observed for VNS [67]. However, given the perception of lower risk and invasive nature of VNS in comparison to CC, it is often preferred as an initial step for surgical intervention in cases of generalized DRE though less efficacious for certain seizure types. Newer approaches for accomplishing CC using less invasive methods may alter this algorithm, and stimulation therapies and CC are probably complementary, not mutually exclusive. Prior case series of patients undergoing CC have included a number of VNS active patients, yet with the efficacy of CC still demonstrable [64].

Deep Brain Stimulation

Deep brain stimulation (DBS) targeting the anterior nucleus of the thalamus (ANT) was recently approved by the FDA for adults with focal DRE. Long-term data has shown continued improvements in efficacy over time with a median decrease in seizures of 69% and 68% of patients experiencing ≥ 50% reduction in seizures by 5 years [72]. Stimulation of ANT likely modulates the limbic pathway, and data suggests greater efficacy for epilepsies of frontal or temporal origin [72]. Some investigators have argued in favor of targeting the centromedial nucleus of the thalamus (CMT) for generalized epilepsies, as reciprocal connections with the anterior cingulate and frontocentral cortex are more predominant. Preliminary data from limited case series suggests that DBS for the CMT may be a possible intervention for generalized DRE, though larger patient experience is needed [73].

Resective Surgery

Cases classified electrographically and clinically as generalized epilepsies occasionally have concurrent seizures with

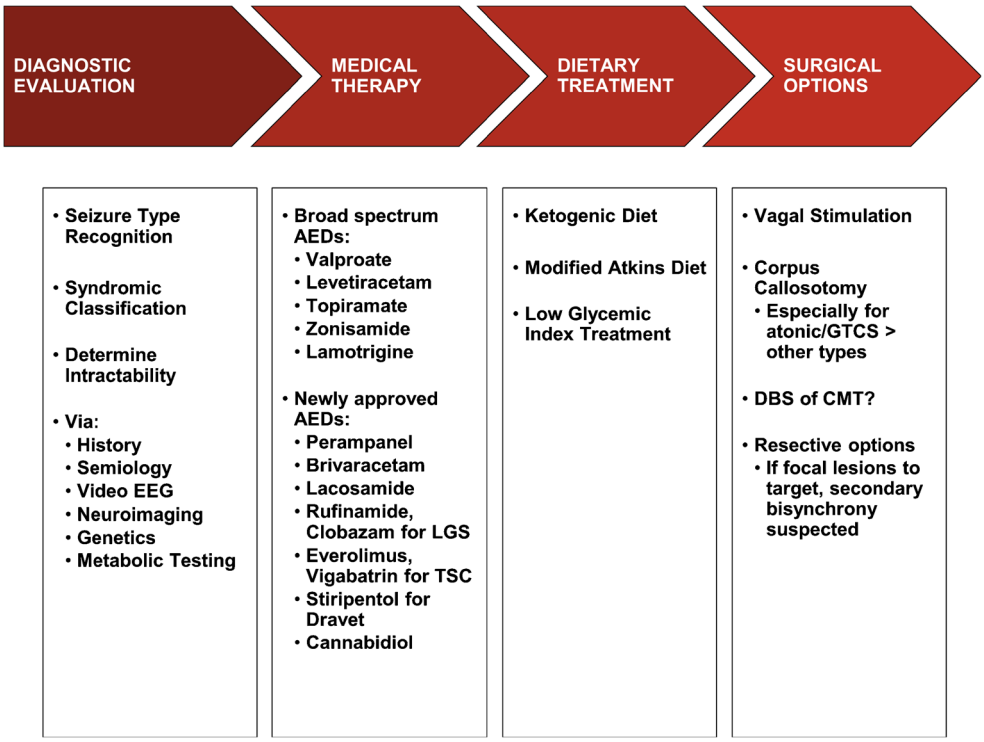

Fig. 1 A treatment algorithm for intractable generalized epilepsy

focal lateralizing semiology and electrographic features. Conversely, the various etiologies underlying a generalized epilepsy syndrome may present with similar phenotype, even in the presence of relatively focal lesions on neuroimaging. As reported by Wyllie et al. in 2007, in selected cases where congenital or early acquired focal lesions are identified (such as MCD or cystic encephalomalacia), resective neurosurgical intervention may still yield promising outcomes despite the presence of widespread electrographic abnormalities [74•]. Of 50 such cases of adults and children undergoing focal resective surgery or hemispherectomy despite generalized or bilateral EEG findings, 72% of patients were rendered seizure-free with a median 2 year follow up. A large case series including 90 pediatric patients with LGS with generalized or multiregional EEG abnormalities reported 50% of patients being rendered seizure-free with resective surgery at an average of 6 years follow-up [75•]. Resective surgery is usually undertaken if a radiographic lesion has plausible correlation with at least some of the patient's seizures by semiology, lateralized predominance of epileptiform findings on EEG, concordant functional neuroimaging, and when the seizures are severe enough to warrant the risk.

In TSC which is often associated with LGS, a predominance of spasms or tonic seizure types, and diffuse ictal EEG findings, the data still appears to indicate favorable outcomes with early surgical intervention [76]. Other etiologies such as watershed or porencephalic lesions may also respond to resective surgery, despite widespread or generalized EEG abnormalities and tonic seizures [77]. Invasive EEG methods such as subdural electrodes or SEEG with electrodes placed stereotactically in and around lesions of interest may help to delineate seizure onset areas from those of rapid propagation [78, 79]. Combining diagnostic methods like SEEG with less invasive ablative approaches, such as LITT, may be effective and may offer the possibility of lower risk of complication and better tolerability [78, 80]. Expectations for seizure freedom are obviously tempered in this patient population by the frequently encountered scenario of multifocal lesions, multifocal or rapidly bisynchronous epileptiform discharges, longstanding epilepsy, and cognitive or functional abnormalities indicative of widespread cortical dysfunction.

Conclusion

For many years, the options for medical, dietary, and surgical intervention for generalized DRE patients had been comparatively limited in relation to treatments for focal DRE. With the advent of new AEDs, changing legal stances on cannabinoids, more permissive dietary options, less invasive surgical options, and increasing experience with neurostimulators in this patient population, clinicians have even more reasons to insure patients are presented with the latest therapeutic options and are achieving optimal seizure control. A treatment algorithm for intractable generalized epilepsy is proposed in Fig. 1.

Compliance with Ethical Standards

Conflict of Interest Sean T. Hwang, Simona V. Proteasa, Aradia X. Fu, and Scott J. Stevens each declare no potential conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- •• Of major importance

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