



Review Article

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Drug-Resistant Epilepsy; An Overview on Management and Treatment

Fatemah O. Kamel^{1*}

¹Department of Clinical Pharmacology, Faculty of Medicine, King Abdulaziz University, Jeddah, Saudi Arabia.

*Email: foakamel@kau.edu.sa

ABSTRACT

Epilepsy is one of the most prevalent chronic neurological illnesses. Presently, the provision of symptomatic medicine is the treatment method for epilepsy. The majority of patients can attain seizure independence during the first two medication trials. Therefore, pharmaco-resistant individuals are those who cannot get an adequate therapeutic response. However, the range of efficacy, safety, and tolerability, the diversity of seizures and epilepsies, the frequency of comorbidity, and tolerance associated with the administration of anti-seizure medicines (ASMs) renders medicating these patients rather challenging. Since medicines with different and potentially additive mechanisms of action as well as improved safety and efficacy profiles than first-generation ASMs have been developed, rational polytherapy has become increasingly important in the second, third, and final-generation ASM period. Recent insights into ASM utilization have spotlighted critical clinical and pathogenetic concerns linked to drug-resistant seizures. Pharmacogenetics, elucidating genetic factors influencing drug response, has also emerged as a promising avenue. Additionally, there is a growing interest in non-pharmacological interventions to complement or augment medication strategies.

Key words: Antiseizure medications (ASMs), Comorbidity, Drug-resistant epilepsy (DRE), Pharmaco-genetics, Pharmaco-resistance

INTRODUCTION

The International League Against Epilepsy (ILAE) defines drug-resistant epilepsy (DRE) as an incapability of two well-tolerated, adequately chosen, and used anti-seizure regimes, either monotherapy or in combination, to trigger sustained seizure independence [1]. Whilst the heterogeneity of DRE patient profiles is similar to the absence of an agreed definition of anti-seizure medicines (ASMs) success in attaining seizure independence, comparing therapeutic studies and defining practice standards remains difficult. Pharmacological treatment should be suitable for the syndrome of epilepsy as well as seizures taken up to at least 6 months at a sufficient dose [2]. The patient's response, the duration of the disease, and the medication's acceptability all influence the best effective dosage range and frequency of delivery. Moreover, adverse side effects further reduce the range of ASMs available [3]. As a result, rather than being a collection of people with the same condition, people with DRE reflect a spectrum of different clinical aspects and neurological images, necessitating a streamlined process to a variety of challenges that we will try to focus on in more detail. This review's objectives are to present a concise overview of the key pathogenetic and clinical concerns related to DRE, as well as to examine the potential of newly developed ASMs, their possible uses in real-world settings, and alternative non-pharmacological therapies for DRE patients.

Antiseizure medications

The U.S. Food and Drug Administration has also approved medications for the management of prevalent epileptic episodes (FDA) throughout the previous two decades (**Table 1**).

Table 1. Anti-seizure medicines and their mode of action.

Drugs	Mode of Action (MOA)
Brivaracetam	Unknown Mechanism for selective affinities for synaptic vesicle protein 2A (SV2A)
Carbamazepine	Block sodium channels, exact MOA unknown
Divalproex sodium	the notion to inhibit GABA transaminase, thus mounting the concentration of GABA. Also inhibits histone deacetylase 1.
Eslicabazepine acetate	Block voltage-gated sodium channels
Ezogabine	Activator of KCNQ ion channels
Gabapentin	Unknown MOA
Lamotrigine	Thought to cause inhibition of voltage-gated sodium channels, unknown MOA
Levetiracetam	Regulates the ejection of chemicals by interacting with synaptic vesicle protein receptors.
Locasamide	Increases delayed sodium channel inactivation as well as interacts with protein 2 of either the collapsing response mediator (CRMP-2)
Oxcarbazepine	Blocks voltage-gated sodium channels
Perampanel	AMPA-type glutamate receptor antagonist
Pregabalin	Modulates voltage-gated calcium channels
Rufinamide	Prolong inactivation state of sodium channels
Topiramate	Block voltage-gated sodium channels, increase the activity of GABA-A receptor subtypes, inhibit carbonic anhydrase
Vigabatrin	Irreversible enzyme-activated GABA transaminase inhibitor
Vigabatrin	Irreversible enzyme-activated GABA transaminase inhibitor
Zonisamide	Thought to block sodium channels and reduce voltage-dependent, transient inward currents.

Drug-resistant epilepsy

Recent epidemiological systematic research reported the total incidence percentage such as DRE ranged from 0.06 to 0.51%, and the pervasiveness ranged from 0.11 to 0.58%. The pooled estimated predominance across the investigated studies would have been 0.30 (95% CI: 0.19-0.42), which compares favorably to what has typically been documented in the study. In adults, the pooled incidence percentage was 0.34% (95% CI: 0.06-0.62), and it was 0.15 (95% CI: 0.11-0.19) in minors, for a total pooled prevalence of 20% (95% CI: 0.14-0.27) [4]. As an added complication, even individuals appropriately diagnosed as pharmaco-resistant might have extended periods of full remission followed by relapses. However, among individuals with a 12-month seizure remission phase in a research cohort together with adults with DRE, the probability of experiencing a seizure remained significant (71.2% after five years). As a result, it is prudent to be cautious while considering the possibility of long-term remission [5].

Risk factors

DRE has already been associated with the occurrence of neuropsychiatric disorders or cerebral impairment, a history of protracted febrile seizures, and particular electroencephalogram (EEG) abnormalities. DRE has been associated with the age at the epilepsy start (one year), the etiology, abnormal neuroimaging, the presence of these abnormalities, and the coexistence of these conditions [6]. The chance of developing DRE is thought to be greater during cases when seizures initially become visible in early childhood as opposed to in cases where epilepsy first appears later in life. The incidence of pharmaco-resistant epilepsies is relatively low in idiopathic epilepsies compared to epilepsies spurred on by structural anomalies including cortical dysplasia, mesial temporal sclerosis, tuberous sclerosis, or vascular lesions. The risk of focal seizures is thought to be greater than that of generalized seizures [6]. Contradictory results have been found when looking at the role of family history, although, no associated risk factor of gender [6]. More than 50% of a cohort of newly diagnosed patients such as all forms of epilepsy was free from a seizure after a single ASM treatment, roughly fifteen percent turnout to seizure-free on the course of management using a 2nd or 3rd drug, and just 3 percent of

epileptic cases were managed by therapy with two medicines. This provides more evidence of management linking refractory epilepsy to be deficient in response to the first-line ASM [7].

Pathogenesis

Drug resistance etiology is likely diverse and complicated [2]. The hypothesized drug resistance pathways, which also include genetic and disease-related ones, may be interrelated.

The "transporter hypothesis" states that independent of the site of such an ASM's action increased multidrug efflux protein expression or function decreases the efficacy of ASMs in human epileptic brain tissue and DRE animal studies [8]. Due to its broad substrate specificity, the ATP-dependent P-glycoprotein (P-gp) contributes to restricting drug entry into the brain. Since the chemical structures of ASMs and P-gp substrates are similar, increased production of P-gp and other efflux pumps may inhibit some ASMs from passing through the blood-brain barrier (BBB). A multi-drug-resistant resistant epileptic phenotype will arise regardless of this [9].

According to the "pharmacokinetic theory," efflux transporter over expression is concentrated in decreasing the dose of ASM that is capable of permeating the BBB most likely in peripheral organs like the liver, colon, and kidneys [10].

Conversely, the "intended hypothesis" proposes that perhaps the target molecules of ASMs incur modifications as a result of acquired epilepsy lowering their responsiveness to therapy [11]. This concept is mostly based on carbamazepine (CBZ) research on voltage-dependent sodium channels in hippocampus neurons and mesial temporal lobe epilepsy (TLE). The use-dependent inhibition of voltage-sodium channels of dentate granule cells by CBZ was eradicated in patients with CBZ-resistant epilepsy when contrasted to neurons from individuals without mesial TLE. Using pilocarpine rodent models, the same results have been seen for CBZ and phenytoin (PHT) blocking voltage-sodium channels [11], but not for other ASMs except lamotrigine (LTG) and valproic acid (VPA) [12]. Furthermore, neurodegenerative changes have been recognized via the persistence of epilepsy as well as axonal sprouting, synaptic rearrangement, neurogenesis, and gliosis, which are the foundation of the "neural network theory" [13] However, these modified changes in the creation of an aberrant neuronal system, which leads to ASM resistance. This view was supported by hippocampal sclerosis, which is assumed to have a causative role in the formation of pharmaco-resistance with TLE, and Resistance is frequently reversed by surgical excision [14]. However, not all epileptic patients exhibit refractoriness caused by changes in the neural state, indicating that additional causative variables must be present [9].

On the other hand, the "intrinsic severity theory" views pharmacoresistance as an essential element of epilepsy that would be related to the intensity of the condition [15]. While it is not the only predictor, high seizure frequency is a good indicator of pharmacoresistance. According to the "genetic theory," differences in gene single polymorphisms account for the diversity in epileptic patients' susceptibility to pharmacoresistant [16]. This theory is predicated on the idea that patients with epilepsy have an endogenous variable that reduces their chances of managing seizures using ASMs.

Neuroinflammation and BBB failure may both play essential roles in generating and maintaining epileptic activity [17, 18]. Within comparable tissue regions, a neuroinflammatory response typically happens along with a BBB malfunction. P-gp is induced in brain arteries and astrocytes in all these situations. However, with DRE and animal model systems of acquired epilepsy, neuronal inflammation and failure of BBB were therefore markers of an epileptogenic zone [10]. Microglia and astrocytes have critical roles in the production and maintenance of the inflammatory reaction to epileptogenic injury or seizures; additional factors include neurons, BBB cell components, and leukocytes [19]. Additionally, it has been found that specific inflamed molecules and pathways influence the results of various epileptic experimental models [20].

Pharmacogenetics of drug-resistant epilepsy

Drug-resistant epilepsy is most likely caused by hereditary factors that alter the pharmacodynamic and pharmacokinetic aspects of the medications utilized. Genetically predetermined polymorphism of certain microsomal enzymes, including such P-gp or multidrug resistance-associated protein (MRP), cytochrome P450 family 2 subfamily C member 9 (CYP2C9) as well as cytochrome P450 family 2 subfamily C member 19 (CYP2C19), as well as disorders of the pharmacodynamic feature of neurotransmitter gamma-aminobutyric acid (GABA) receptors and ion channels.

Drug transport proteins

P-glycoprotein

P-glycoprotein (P-gp), moreover recognized as multidrug resistance-associated protein 1 (MDR1), is a member of the ATP-binding cassette transporter (ABC) family of membrane proteins. P-gp was initially identified to induce tolerance to anticancer medications in tumor cells, but its appearance has since been identified in numerous other tissues [21, 22]. In a major way, this protein modifies the drug bioavailability following mouth administration, the infiltration into particular tissues, and the eradication of numerous medicines and their metabolites [23]. Many studies [24-26] demonstrate that P-gp overactivation causes anticonvulsant drug resistance by reducing the brain's uptake of these medications. This occurs because P-gp is overly active, removing substances from the BBB and returning them to the bloodstream. Moreover, tariquidar and other highly selective drugs that inhibit P-gp activity have been shown in experimental studies to boost Phenytoin's effectiveness as an anti-convulsant [27] while also assisting in overcoming phenobarbital resistance [16]. In contrast to patients in the control group, Tishler *et al.* [28] discovered that MDR1 gene expression in the epileptic focus was more than ten times greater among individuals who had surgery to treat drug-resistant epilepsy.

Thus, the genotype i.e. C3435C of the MDR1 gene has been linked to medication resistance in epilepsy [29], although this has not been verified by other investigations [28-31]. While Alpmann *et al.* [32] discovered that the MDR1 C3435T and G2677AT polymorphisms are just not related to multi-drug resistance, but that the CC3435/GG2677 compound genotype may change treatment efficacy, drug-resistant epilepsy has been linked to the C3435T and G2677T/A polymorphisms in the Polish population [33]. Likewise, MDR1 C3435T polymorphism and drug-resistant epilepsy in toddlers were examined by Lv *et al.* [34]. A significant correlation between the MDR1 C3435T polymorphism and the general chance of drug resistance was not found, according to the analysis.

ABCC2 and ABCG2 polymorphisms

Gene variants in members of the ATP-binding cassette superfamily, such as ABCC2 and ABCG2, influence how they react to ASM, but the validity of this information is debatable and ambiguous [34-37]. In an attempt to provide compelling proof for the association amongst the frequent mutations in ABCC2 and ABCG2 responses and ASM in epileptic patients, meta-analysis researches were done [38]. There are numerous functional genetic variants in ABCG2, which is located on chromosome 4q22.1, including rs2231137 and rs2231142. In the general mixed community, it has been demonstrated that the ABCC2 rs717620 polymorphism is linked to ASM resistance.

RLIP76/RALBP1

Evidence from Awasthi *et al.* [39] opposes the glycoprotein RLIP76/RALBP1 is involved in the transport of ASM, which in turn contributes to the progression of restricting the inflow of these treatments in the nervous tissue and ultimately results in resistance to therapy. Though, later investigations failed to replicate these findings [40, 41].

Enzymes that metabolize drugs

It is widely accepted that drug metabolism steps have an impact on drug availability at the site of action, toxicity, excretion route, and blood concentration of the drug. Enzymes belonging to the cytochrome (CYP) P450 family are responsible for the metabolism of the vast majority of pharmaceuticals. The initial step in the metabolism of foreign compounds is carried out by the cytochromes P450 family 2 (CYP2), the most varied of the 18 cytochromes P450 families discovered so far. There are several polymorphic enzymes present. In terms of clinical relevance, CYP2C9, CYP2C19, and CYP2D6 stand out as the most significant [42].

Two cytochromes P450 enzymes, CYP2C9 and CYP2C19, play a significant role in the biotransformation and elimination of medicines, including ASM, via oxidation processes and glucuronidation. Their genetic polymorphism impacts the rate at which they metabolize drugs, which may cause variations in their susceptibility to the effects of such drugs as well as significant idiosyncratic responses and even toxic symptoms [42]. The CYP2C9 gene has 13 alleles, with CYP2C9*2 and CYP2C9*3 resulting in mutations in the CYP2C9*1 coding sequence. This is linked to decreased phenytoin metabolizing enzyme activity [43]. Van der Weide *et al.* [44] found that the dosage of CYP2C9*3 required to attain therapeutic blood concentration occurred 37% less in patients with CYP2C9*3 than in patients with CYP2C9*1.

In the research of Lopez-Garcia *et al.* [45], polymorphisms of CYP2D6, CYP2C9, CYP2C19, and CYP3A4 were detected in children with DRE. According to the findings, the CYP 3A4*1B allelic mutation is a major susceptibility indicator for the emergence of drug resistance. ASM responsiveness may be influenced by SNPs, CYP2D6 haplotypes, and CYP2C19 haplotypes [45]. The CYP3A5*3 polymorphism and C3435T polymorphism in the MDR1 gene and pharmacological seizures were not associated, according to Emich-Widera *et al.* [46].

Management of patients with drug-resistant epilepsy: a practical approach

Given approximately half of the individuals that still suffer from epilepsy obtain durable seizure control (>12 months) with a single medication regimen, monotherapy is often the primary line of treatment for newly diagnosed patients with epilepsy [47]. Some authorities recommend waiting until two or three different treatments have failed before trying polytherapy [48, 49]. After the initial medicine monotherapy failed, new study indicates that duo therapy should be chosen as an alternative to achieve seizure remission of 15-20%, with about 60% of patients potentially obtaining seizure independence after the second drug trial [50].

The International League Against Epilepsy (ILAE) advocates that patients be referred to specialist epilepsy clinics if they do not react to a second pharmacological trial (either monotherapy or duo therapy) [1]. Re-evaluation (e.g., to the full video, neuroimaging) is required to determine the proper epilepsy type diagnosis or clear out the causative factors of pseudo-pharmaco-resistant. If patients with epilepsy who may be surgically treatable, such as those with focal epileptogenic lesions, are sent to specialist facilities without delay, they have a better chance of seizure remission (about 60-80%) compared to if they carry out more pharmacological trials. If the lesion cannot be surgically removed completely without causing neurologic morbidities, a lower rate of remission is anticipated; therefore, systematic studies of a second duo therapy or a triple therapy should have been carried out [50]. As a result, choosing patients who might benefit from polytherapy is a critical step that has important practical consequences for improving seizure control. However, it is best to avoid increasing the number of medications from three to four, since doing so significantly increases the risk of adverse events (AEs) without significantly enhancing the ability to control seizures [51]. Whether of fifth and sixth drug trials using double, triple, or quadruple treatment fail, it is time to consider alternatives. Attempts might be made to try the vagus nerve stimulator (VNS) or the ketogenic diet. There must be a thorough analysis of the patient's prior ASM treatment, including the dosages used, the medications' effectiveness, and the complete range of adverse effects.

Pharmacological therapy in drug-resistant epilepsy

When treating patients with refractory epilepsy, pharmacological treatment is the gold standard. However, poly-therapy must be considered cautiously, taking into consideration the risk-benefit ratio in order to meet patient compliance requirements as well as effectiveness and tolerability. Due to a high frequency of adverse effects (AEs), the initial generation of ASMs had substantial restrictions regarding their amount, modes of action, pharmacokinetics (strong inducers or inhibitors), and endurance profile. For patients with untreated generalized tonic-clonic and/or partial seizures, a single randomized controlled trial (RCT) compared the initial treatment regimen of CBZ monotherapy with CBZ and VPA combination therapy. Even though the results were not statistically significant, the combination therapy indicated relevant pharmacokinetic drug interactions [52].

Polytherapy's goal has been shown in patients with pharmaco-resistant was to find ASMs amalgamation with the best balance of benefits and adverse effects [52]. There are not enough human clinical trials to determine the optimal permutation of ASMs; thus, the selection of a 2nd or 3rd medicine in sensible polytherapy should also take into account animal research and empirical factors [53]. Combination therapies should have both a supra-additive impact (synergy effect) against seizures and a neurotoxic antagonism or neurotoxic infra-additive effect [54]. When compared to the combined treatment of a sodium-channel blocker and a medicine with a different mechanism of action, such as a GABAergic agent, studies contrasting agents with sodium-channel blocking actions experienced a higher frequency of adverse events (AEs) and worse efficacy [55, 56]. VPA plus LTG is the most promising combination, with strong evidence of synergy from human trials. Multiple studies indicated a significantly higher response rate when LTG was used as an adjunct treatment with VPA compared to when LTG was used with CBZ or PHT, suggesting a synergistic interaction between these ASMs. In children with severe absence seizures, combining VPA with ethosuximide (ETX) proved more successful than either treatment alone. LTG-LEV [57] and lacosamide (LCM)-LEV [57] are two more combinations that have been tested in a group of individuals with focal seizures [58, 59]. A synergistic impact may arise from the fact that various ASMs have diverse modes of action when combined. While LCM

increases the delayed inactivation of voltage-gated sodium channels, LEV controls neurotransmitter release via binding the SV2A protein found on synaptic vesicles [57]. LTG-TPM and VPA-LEV are associating regimens of adolescents may be helpful, however, the data is weak [60].

The addition of stiripentol (STP) to the standard treatment of clobazam (CLB) and vigabatrin (VPA) for children and adolescents with Dravet syndrome (DS) is supported by a solid body of data. Starting in Europe in 2007, STP has since gained approval as a supplementary treatment for DS in Japan (2012), Canada (2012), and the United States (2018) [61]. Youthful patients with DS who were already being treated with VPA and CLB in two randomized controlled studies in 2000 [62] and 2002 [63] showed a considerably greater response rate with STP than those treated with a placebo. Subsequent observational retrospective and prospective long-term investigations corroborated these outcomes in requisites of seizure control, a decrease in protracted seizures, episodes of status epilepticus, and hospital stay. In DS, STP's anti-seizure effects may arise from two distinct processes. Both the pharmacokinetic effect of STP (increasing CLB active metabolites) and STP seem to have a different mode of action than benzodiazepines, which is associated with enhanced acidergic transmission via post-synaptic GABA receptors [61]. Eslicarbazepine acetate, gabapentin, and zonisamide are three more recent ASMs that have shown potential as additional treatments for DRE [53]. Despite the growing enthusiasm for new ASMs and recommendations for their usage in DRE, no new ASM has yet shown significant effectiveness advantages over older, more established ASMs in direct comparative trials [64].

Drug-drug interactions and varying pharmacokinetic and adverse effects profiles are additional concerns when using sensible polytherapy. Earlier, it has been established that previous ASMs have several connections with other medications (whether ASMs or other pharmaceuticals), most of which are mediated through the drugs' effects on the cytochrome P450 as enzymatic inhibitors or inducers. For instance, VPA works as a powerful enzymatic metabolic inhibitor, meaning it may decrease LTG clearance, raising LTG haematic level and, by extension, the likelihood of LTG-induced hypersensitivity or tremor development [65]. For this competition, the doctor has to titrate LTG steadily, beginning with smaller dosages of the most recent. In contrast, CBZ, phenobarbital (PB), and PHT are inducer enzymes that may lower concentrations of anticoagulants, oral contraceptives, or immunosuppressants. Not only that, but these more senior ASMs have a wide variety of AEs, from hepatotoxicity and encephalopathy linked with VPA to bone marrow suppression caused by CBZ, PHT, and PB [66].

However, because of their better tolerability profiles and reduced pharmacokinetic interactions (many which are weak enzyme inducers or inhibitors), the new ASMs are excellent choices for combination therapy [67]. Because of its low potential for drug interactions, LEV is often used with zonisamide and thiopurine in polytherapy. Individuals with high QT syndrome should not use TPM, zonisamide, or LEV; individuals with neuropsychiatric comorbidities should not take TPM, rufinamide, or retigabine; and patients using TPM, rufinamide, or retigabine may be at an elevated risk for anxiety, depression, and psychosis [53]. It's worth noting that no proof using several therapies simultaneously may lead to more adverse events AEs. Patients receiving polytherapy were capable of tolerating a larger cumulative dosage of drugs (TDL, ratio of given every day dose as described by WHO) than some of those receiving monotherapy, and there was no perceptible difference in the risk of adverse outcomes (AEs) between patients who received monotherapy and those receiving polytherapy.

Some authors have hypothesized that the selection of ASMs, their doses, and the individual's predisposition all have a role in the development of AEs in polytherapy, rather than the number of medicines being used [68] (**Table 2**). As a result, selecting the best ASMs regimen for a pharmaco-resistant patient requires careful consideration of a wide range of factors, considering patient-specific factors such as age, compliance, comorbidities, and concurrent drugs in addition to the pharmacological and pharmacokinetic properties of ASMs. Epilepsy syndrome and the different kinds of seizures should help the doctor decide which ASMs are best for treating DRE.

Table 2. ASMs combinations in several human studies

Drug combinations	Seizure types and/or epileptic syndromes
VPA + LTG [60]	Focal refractory seizures; no-specified DRE; possible combination therapy for absence seizures [69].
VPA + ETX [56]	Absence seizures
LTG + LEV [57]	Idiopathic generalized epilepsy and post-traumatic focal epilepsy

LCM + LEV [58]	Focal onset seizures in adults.
VPA + CLB + STP [61, 62]	Dravet Syndrome

VPA (valproic acid); LTG (lamotrigine); ETX (ethosuximide); CBZ (carbamazepine); LEV (levetiracetam); CLB (clobazam); LCM (lacosamide); STP (stiripentol).

Emerging antiseizure medications to overcome drug-resistant epilepsy

Even though many ASMs have been developed recently, about thirty percent of individuals' who have epilepsy are nevertheless resistant to medication and are in dire need of effective seizure control and improved quality of life [1]. Perampanel (PER) and brivaracetam (BRV) are two recently licensed ASMs for those experiencing focal seizures—more precisely, initial generalized tonic-clonic seizures—with or without secondary generalization. With a broad spectrum of action, PER is a first-in-class, non-competitive amino-3-hydroxyl-5-methyl-4-isoxazole-propionate (AMPA) receptor antagonist. Three double-blind, randomized, placebo-controlled phase III clinical trials (RCTs 304, 305, and 306) as well as one open-label extension experiment (research 307) evaluated the effectiveness of PER in patients with drug-resistant focal epilepsy [70-73]. The basis for the approval of PER for primary generalized tonic-clonic seizures was a double-blind, randomized, placebo-controlled trial (study 332) showing ILAE Class I proof of decreased seizure frequency in refractory idiopathic generalized epilepsy [74].

Currently, BRV is authorized as an adjunctive therapy for individuals with focal onset seizures. Like levetiracetam, BRV binds to SV2A vesicles with a linear pharmacokinetic profile and enhanced affinity. It has been demonstrated that BRV treatment reduces seizure frequency and is well tolerated in patients with drug-resistant focal epilepsy. To draw clear findings on its effectiveness in non-levetiracetam-naïve people and to assess its long-term safety profile, more research is required [75]. Increasing data also supports prescribing it to pediatric patients due to its effectiveness and tolerance profile [53].

CBD, a non-psychoactive cannabinoid derived from cannabis, was recommended as a pure CBD oral solution in combination therapy with CLB for DS and LGS patients two years of age and older in one of the earliest clinical trials [76]. Unlike other recently developed ASMs, CBD is the first drug in this new class of drugs and has a unique molecular structure and mode of action. It is non-psychotropic at clinically relevant dosages, but it acts as an anticonvulsant on many targets, including desensitization of TRPV1 channels, G protein-coupled receptor 55 (GPR55) antagonism, and positive allosteric modulation of GABA_A receptors [76]. CBD has been shown to be safe and effective as an adjuvant medicine in patients with LGS in two phase III randomized, double-blind, placebo-controlled trials. These trials focused on the management of drop attack seizures [77, 78].

A phase II randomized, double-blind, placebo-controlled trial of CBD was conducted in children and adolescents with DS [79, 80]. Similar findings were supported by research on open-label adaptations [81]. In a subsequent meta-analysis, there was no evidence of a dose-response relationship (10 vs. 20 mg/kg/day). However, recent data showed that adjunct treatment CBD at doses of 10 or 20 mg/kg/day led to nearly equivalent decreases in the frequency of convulsive seizures for both dosages, with better safety and tolerability characteristics for the 10 mg/kg/day dose [82].

Conversely, the use of fenfluramine (FFA) as an ASM arose peculiarly, given that it was first licensed as a weight-loss medicine before being removed in 1997 due to cardiac consequences (valvular hypertrophy and pulmonary hypertension) [83]. FFA is an amphetamine derivative that exerts its anticonvulsant action by interrupting serotonin vesicle storage, blocking its absorption from synapses, and modulating the sigma 1 receptor positively. In addition, its metabolite, norfenfluramine, has a high affinity for serotonin receptors in the brain (particularly 5HT_{2C} and 1D; 5HT_{2A} is unclear) [84]. As described in several case studies, FFA has continued to be used in children with various kinds of epilepsy, including pharmaco-resistant individuals (89). With positive results, a group of pediatric neurologists in Belgium proceeded to give children with DS FFA at lower concentrations [85].

Multiple trials including young children with Down syndrome and LGS have evaluated the effectiveness of FFA in seizure management. An approximate 75% reduction in seizure frequency in prospective, open-label research involving patients to DS treated with FFA at a mean dosage of 0.35 (0.16-0.69) mg/kg/day for a median of 1.5 years [86]. The FFA group demonstrated a higher response rate in terms of a decrease in convulsive seizures compared to the placebo group in two multicenter, double-blind, placebo-controlled, randomized clinical trials involving children with Down syndrome treated with STP-inclusive FFA drug regimens (with a variable dose of 0.2 to 0.7 mg/kg/day, maximum 30 mg/die) [87, 88]. Additionally, no

adverse cardiac consequences were reported. Compared to doses of weight-reduction medications (up to 60 mg/day), ASM dosages (20–30 mg/diet maximum) did not cause any cardiac side effects [89].

Anorexia, diarrhea, nasopharyngitis, lethargy, somnolence, and fever were the most prevalent non-cardiovascular adverse effects. Different dosing regimens (ranging from 0.1 to 0.8 mg/kg/day) of FFA for LGS produced the same effectiveness, safety, and tolerability outcomes, but with a lower degree of consistency in terms of the number of clinical studies conducted. Randomized controlled studies are currently continuing; thus, we will be able to validate these findings shortly [84, 87].

In addition to CBD and FFA, Loscher *et al.* address the emergence of promising research on the usage of cenobamate and padsevonil [90]. padsevonil is now undertaking a phase III clinical study in individuals with multidrug-resistant focal seizures [85]. Using the same logic, cenobamate, a recently approved ASM for the treatment of partial-onset seizures in adults, has been investigated; it reduces excitatory sodium present and enhances inhibitory currents through GABA_A receptor regulation [91].

In the era of genomics, “precision medicine” is another intriguing option. The introduction of genomic technology has made it possible to better describe the genetic origin of epilepsy and is gradually altering the classification of epileptic disorders. Different patterns of gene mutations may underlie the same epileptic disease and be accountable for varying drug responses, while mutations of the same gene may result in distinct phenotypes. The number of genes with rare harmful mutations is steadily increasing. These insights have resulted in sensible treatment options, such as a better selection of ASMs from those now available or the repurposing of medicines that were not previously used to treat epilepsy [92].

Certain metabolic abnormalities can be treated in some situations (pyridoxine for pyridoxine-dependent epilepsies, or the ketogenic diet for GLUT1 deficiency) [93], but avoid ASMs that could exacerbate the pathogenic problem (e.g., the administration of sodium channel blocking medications in SCN1A-related DS), or contrast the functional defect brought on by gene mutation using already-existing ASMs (e.g. While most intriguing gene-specific therapies reported are based on case reports or short-term studies, two confirmed applications of this precision medicine are the use of everolimus in Tuberous Sclerosis Complex-associated focal epilepsy and the use of CBD and FFA in Down syndrome [94].

Alternatives to pharmacological treatment in drug-resistant epilepsy

Where it is practicable, surgical therapy is the best and perhaps most successful treatment choice for ASMs in individuals with refractory epilepsy. In some cases, deferring surgery can lower the likelihood that a patient will recover seizure independence; as a consequence, it is critical to suddenly locate patients who may be candidates for intervention, as was stated above. There are now several neuromodulation methods for DRE that are either intrusive, requiring surgical device insertion, or non-invasive, requiring no long-term implantation.

Deep brain stimulation (DBS), receptive capabilities and enhancement (RNS), and continuous sub-threshold cortical stimulation are the other invasive neurostimulation techniques that have received the most study and are the most well-established. (CSCS). Transcutaneous vagus nerve stimulation (tVNS), trigeminal nerve stimulation (TNS), transcranial magnetic stimulation (TMS), and transcranial direct current stimulation (tDCS) are non-invasive options [95, 96]. Regrettably, regardless of the expanding number of neurostimulation devices, there is little understanding of the underlying processes and no agreement across epilepsy centers over when and how to employ these therapies.

In 1997, the FDA authorized VNS as an adjuvant therapy for DRE in the United States, notwithstanding that its use has also been investigated in other medical disciplines (such as melancholy, heart failure, stroke, and tinnitus) [97]. VNS is presently used for adults and children with DRE who are not candidates for the appropriate surgery and suffer from focal or generalized seizures, despite the reality that it was first endorsed for partial-onset seizures in individuals over the age of 12 [98]. Baseline stimulus (open-loop) and magnet mode compose the conventional VNS (on-demand). The device's primary working state is baseline stimulation, wherein intermittent stimulation is prevalent consistently with intermittent interruptions (e.g., the 30s on and 5 min off). By dragging a magnet across the pulse generator during the start of a seizure, a patient can provide additional stimulation [99]. A recent method known as adaptable VNS uses closed-loop auto-stimulation to deliver stimulation when tachycardia, a seizure start marker that occurs in much more than 80% of both generalized and confined seizures, is present [97, 99].

Typically, two weeks after implanting the device, basal stimulation must also start. VNS is well tolerated, and there are no substantial AE distinctions between the two activation protocols. Principal adverse effects

described include hoarseness, cough, dyspnea, discomfort, paresthesia, nausea, and headache [100]. However, prospective observational studies show that VNS may potentially be beneficial for generalized epilepsies [97].

In 2018, the FDA authorized DBS as an invasive non-pharmacological therapy whereas adults >8 years were treated with DRE whilst surgical resection is contraindicated. Moreover, a pulse generator delivers programmed electrical stimulation to deep brain areas proposed with (open-loop) including the anterior nucleus of the thalamus (ANT), hippocampus (HC), the centromedian nucleus of the thalamus (CMT), cerebellum, and globus pallidus via implanted electrodes. DBS is believed to interrupt networks in important regards with seizure propagation thalamic activity was implicated, hence lowering interictal discharges, however, the process is not fully understood [96]. In the previous study, approximately 110 adult individuals with localization-related epilepsy participated in the SANTE (Stimulation of the Anterior Nucleus of the Thalamus for Epilepsy) experiment.

CONCLUSION

It is challenging to compare clinical data and provide recommendations for DRE patients because of their unpredictable and variable remission and recurrence intervals. The pathogenetic hypotheses that have been developed so far, which are mostly based on pre-clinical indication, have not executed a single and thorough justification for medication resistance, but rather just detail distinct pathways that may be responsible for it and maybe the target of future drugs. Despite the risk of adverse effects and medication interactions in polytherapy patients, pharmacological treatment is still the gold standard for long-term seizure control. Following a proper diagnostic classification patient selection for surgery, to select the best treatment regimens for each patient, it is essential to have a sufficient understanding of the pharmacodynamic and pharmacokinetic profiles of the medications, as well as any possible side effects and the most advantageous pharmacological connections. Since medicines with dissimilar and possibly additive mechanisms of action as and improved safety and effectiveness profiles have been developed in comparison to first-generation ASMs, rational polytherapy has become increasingly important in the second, third, and final-generation ASM period. Prior to declaring that a patient is unresponsive to medication therapy, it's critical to reassess the patient's genetic background (when available, genetics may influence the choice of a particular drug over others), and previous drug administration to try future, more effective therapeutic regimens. Electrical stimulation and dietary therapy are examples of non-drug treatments that might work, but they are not long-term solutions.

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