Current Principles in the Management of Drug-Resistant Epilepsy

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Abstract:

Drug-resistant epilepsy (DRE) is associated with poor health outcomes and increased economic burden. In the last three decades, various new anti-seizure medications have been developed, but the proportion of people with DRE remains relatively unchanged. Developing strategies to address DRE is essential. Here, we define DRE and emphasize its relationship to the conceptualization of epilepsy as a symptom complex, delineate clinical risk factors, and characterize mechanisms based on current knowledge. We address the importance of ruling out pseudo resistance and consider the impact of nonadherence on determining whether an individual has DRE. We then review the principles of epilepsy drug therapy and briefly touch upon newly approved and experimental anti-seizure medications.

Key Points

- Epilepsy is a symptom-complex.
- Numerous mechanisms exist for drug-resistant epilepsy.
- Novel therapeutics seek to mitigate drug resistance.

1. Introduction

Epilepsy, a tendency to have unprovoked epileptic seizures, is a common neurological condition with a point prevalence of around 6.3 per 1,000 persons.[1] Mostly, people with epilepsy have good outcomes. Up to third, however, continue to have seizures despite treatment, and they constitute the group with drug-resistant epilepsy (DRE) or chronic epilepsy. The definition of DRE differs across studies, but the pooled prevalence of DRE among people with epilepsy is 25-36%, though the risk may be lower in the elderly.[2-5] People with DRE have high rates of psychiatric and somatic comorbidities and are at an increased risk of premature death, injuries and poorer quality of life.[6-9,10] DRE leads to increased visits to casualty, hospitalizations, length of hospital stay, consultations, and medical expenditures.[11] Despite the launch of several new anti-seizure medications (ASMs) over the past three decades, the rate of DRE remains relatively unchanged. Accordingly, developing strategies to address DRE is essential. Here, we provide a conceptual framework for DRE, characterize the underpinnings of treatment, and provide an update on new therapies.

2. Methods

This is a narrative review. PubMed MEDLINE and Google Scholar were searched in January 2022 with keywords including “drug-resistant epilepsy”, “drug resistant epilepsy”, “antiepileptic drugs”, “anti-epileptic drugs”, “anti-seizure medications”, and “antiseizure medications” to retrieve studies related to the mechanisms of DRE, measures to verify DRE, and existing and emerging therapeutics for DRE. Studies providing primary data were aggregated in a citation manager. Relevant review articles were browsed for additional studies that provided information on the topic of interest.

3. Defining Drug-Resistant Epilepsy

In 2010, the International League Against Epilepsy (ILAE) released a consensus definition of DRE.[12] The framework includes two “hierarchical levels”. Level 1 is a general scheme to categorize response to a given intervention first based on whether the individual attains seizure freedom or experiences treatment failure and then on the occurrence of adverse effects. [12, 13] Appropriate application of this level assumes appropriateness and adequate application of the intervention.[12, 14] Adequate/informative trials depend on the intervention,

duration of exposure, seizure occurrence and adverse effects during the trial period, whether dose was optimized, and, if applicable, reasons for discontinuation.[12] Level 1 forms the foundation for level 2, which defines DRE as a failure of appropriate trials of at least two well-tolerated, appropriately selected, and properly used – whether in monotherapy or combination – ASM regimens to achieve sustained seizure freedom.[12, 13] Well-tolerated implies freedom from disabling side effects.[14] Appropriately selected means that the seizure or epilepsy type is responsive to the ASM.[14] Properly used indicates that adequate doses must be used for significant lengths of time before discontinuing the medication trial and that treatment failure must not solely result from a lack of adherence.[14] The two ASM caveat in Level 2 arises from suggestions that the likelihood of treatment success of subsequent regimens is reduced if complete seizure control is not attained with two ASMs.[15, 16] Newer data suggests that although epilepsy unsuccessfully controlled by the first ASM has a 1.73 times greater odds of not responding to treatment for each ensuing medication regimen, 14% of the remaining population of individuals with DRE become seizure-free with the sixth ASM.[17] Overall, both levels of the consensus definition has a high degree of inter-rater reliability.[18] Notably, the definition is dynamic rather than static.[12, 19]

4. Epilepsy as a Symptom-Complex

Epilepsy is the tendency to have unprovoked seizures secondary to brain pathology or system dysfunction.[20] The aetiology, demographics, clinical presentation, treatment strategies, and prognosis of epilepsy vary considerably.[21] Thus, epilepsy is more appropriately described as a symptom-complex with multiple risk factors and a strong genetic predisposition rather than a disease with one expression and aetiology.[22, 23] Epilepsy includes a spectrum of disorders, all of which result in epileptic seizures with associated biological, psychological, and social conditions, resting on comorbidities.[24, 25] Additionally, epilepsy comprises a portion of the functional spectrum of brain conditions involving abnormal paroxysmal neuronal or glial functioning, including neurologic and psychiatric disorders, all likely precipitated by a tendency toward paroxysmal activity.[21] DRE forms part of the epilepsy continuum, with distinct clinical risk factors and genetic predispositions.

5. Clinical Risk Factors for Drug-Resistant Epilepsy

Risk factors for DRE have been identified. High seizure frequency around onset and the presence of a structural cause, are common predictors of DRE.[15, 16] Individuals with febrile seizures, multiple seizure types, symptomatic etiology, status epilepticus, and abnormal EEG may be more predisposed to DRE.[3] Predictors based on the age of onset of epilepsy have also been identified. In children younger than one year, high seizure frequency before diagnosis or treatment, abnormal neuroimaging; abnormal EEG; symptomatic epilepsy; mixed seizure types; history of status epilepticus; and intellectual disability predict poor prognosis.[26-29] In adolescents, focal epilepsy, developmental delay, or psychiatric disturbances predict DRE.[30] In adults, symptomatic focal epilepsy mainly due to mesial temporal sclerosis, consciousness impairment during seizures, multiple seizure types, tonic-akinetic seizures, and EEG abnormalities predict DRE.[31, 32] Similarly, predictors have been identified in specific epilepsy subtypes. Focal seizures with onset before age one year, infantile spasms, and infantile spasms incompletely responsive to therapy are associated with a greater likelihood of drug resistance in people with tuberous sclerosis complex.[33] Children with juvenile myoclonic epilepsy with psychiatric symptoms or a combination of seizure types are predisposed to drug resistance.[34] Predictive analytic tools have recently been utilized to identify people with DRE.[35, 36]

6. Mechanisms of Drug-Resistant Epilepsy

The mechanisms of drug resistance are most likely variable and multifactorial based on the aetiology and the site of ASM action.[13, 37] Hypotheses regarding the mechanisms of DRE may be categorized as disease-related, drug-related, or genetic, all of which may be connected.[38] It has been suggested that at least the following four criteria must be satisfied for a drug-resistance mechanism to be accepted: the mechanism must be detectable in epileptogenic brain tissue, have appropriate functionality, be active in drug resistance, and curb drug resistance when inhibited.[39] Much of the current thinking on these mechanisms is mainly based on circumstantial clinical evidence with limited preclinical support[38] Assessing the underlying mechanisms of DRE is essential to stratify people who may have a poor response to ASMs and develop new therapeutic approaches.[40-42] Commonly cited mechanisms are reviewed below. Multiple mechanisms may act concurrently or interact on the level of the individual, complicating the development of methods to address drug resistance.[38, 43]

6.1.Target Hypothesis

ASMs must act at least one target molecule in the brain, including voltage-dependent ion channels, neurotransmitter receptors, and transporters or enzymes.[44] The target hypothesis asserts that epilepsy-induced alterations in the structure or function of brain targets of ASMs reduce treatment sensitivity.[45] This hypothesis arose from a study demonstrating that carbamazepine-induced use-dependent block of voltage-dependent Na+ channels of dentate granule cells was lost in people with carbamazepine-resistant temporal lobe epilepsy (TLE) and a pilocarpine rat TLE model.[46] A follow-up study appeared to confirm these findings by determining that effects of phenytoin on fast recovery from Na+ channel inactivation of hippocampal granule cells was reduced in a pilocarpine rat model of TLE. At the same time, lamotrigine slowed the time course of recovery from fast inactivation with no difference between rats with and without epilepsy.[47] Another study demonstrated that loss of sensitivity to carbamazepine and phenytoin was less pronounced in hippocampal CA1 neurons than dentate granule neurons, indicating that target mechanisms are specific to the cell type and ASM.[48] Voltage-gated Na+ channels play an essential role in the generation and propagation of action potentials. Alterations are either loss-of-function or gain-of-function mutations related to channel inactivation.[49, 50] Studies have reported alternations in beta subunits of voltage-gated Na+ channels, resulting in protein misfolding or abnormal channel expression, with slowly inactivating channels that increase Na+ currents and promote reduced drug sensitivity.[49, 51-54]

Other receptors, including voltage-gated Ca2+ channels, $GABA_A$ receptors, and glutamate receptors, have been explored in cells and animal models. Voltage-gated Ca2+ channels have also been examined as a contributor to DRE through their role in the firing of action potentials and role of Ca2+ as a secondary messenger.[55, 56] Alterations in these channels can increase activity and surface expression, precipitating hyperpolarized potential leading to drug resistance through recurrent seizures.[57-60] Additionally, $GABA_A$ receptors have been implicated in DRE. These receptors are inhibitory in the adult brain but depolarize during the neonatal period. In cases of traumatic brain injury, increased inhibition may cause neural synchrony or aberrant network disinhibition, resulting in recurrent seizures and DRE.[61-65] Similarly, alterations of $GABA_A$ receptors, such as transpositioning of subunits, may result in the absence of ligand-binding sites for ASMs such as benzodiazepines.[63, 66] Glutamate receptors have also been explored. Glutamate receptors and $GABA_A$ receptors act in opposition to each

other.[63] Glutamate N-methyl-D-aspartate (NMDA) receptor activation during seizures leads to clathrin-mediated internalization of $GABA_A$ receptors in a Ca2+-dependent manner, reducing inhibitory neurotransmission and potentially preventing.[63, 67-69] Lastly, antibodies to voltage-gated K+ channels are present in 6% of people with long-standing epilepsy. Still, it is unclear whether the antibodies are pathogenic or secondary to another pathological process.[70] At present, the primary criticisms of this model are limited data and an inability to explain why people with DRE do not respond to ASMs with different targets.[38, 42, 71]

6.2.Drug Transporter Hypothesis

Membrane efflux transporters may play a role in resistance by reducing the concentration of ASMs at intended targets.[72] The drug transporter hypothesis was proposed after findings that P-glycoprotein and the gene encoding it, MDR1 / ABCB1, was elevated in capillary endothelium and astrocytes from brain samples of people with intractable epilepsy undergoing surgery.[73] Since then, the theory has expanded to include the multidrug-resistance associated protein (MRP1/2), breast cancer resistance protein (BRCP) in addition to P-glycoprotein, all of which are known multidrug efflux transporters at the blood-brain barrier.[63, 74-76] Polymorphisms of MDR1 are the most reported genetic predictor of DRE.[5] Others have found overexpression of MDR1 and other multidrug resistance proteins in epileptogenic brain tissue of people with DRE.[42] Hippocampal sclerosis, cortical dysplasia, and dysembryoplastic neuroepithelial tumours show overexpression of ABCB1 and MRP1.[77] Functional in-vivo positron emission tomography (PET) studies using [^{11}C] verapamil, which acts as a substrate and inhibitor of P-glycoprotein, suggested reduced uptake in people drug-resistant compared to healthy and seizure-free individuals.[78-80] The only randomized controlled trial of verapamil in DRE showed no difference in seizure reduction relative to placebo.[81] Still, overexpression of multidrug efflux transporters in astroglial end-feet may represent another barrier when the endothelial blood-brain barrier function during transient, local disruption from seizures, decreasing the extracellular concentration of ASMs near the epileptogenic zone and triggering drug resistance.[38, 82] Some investigators have hypothesized that the expression of drug transporters such as P-glycoprotein may mark the presence of a site of drug resistance.[83] This hypothesis requires additional investigation. [38]

6.3.Pharmacokinetic Hypothesis

The pharmacokinetic hypothesis postulates that overexpression of efflux transporters in peripheral organs decreases ASM levels in people with DRE, reducing the amount available to cross the blood-brain barrier.[84] The initial formulation of the hypothesis was based on case studies[84], and existing data do not support this hypothesis. Studies show persistently low ASM levels in people with DRE, which may relate to drug-metabolizing enzymes rather than efflux transporters given the cytochrome P450 enzymes occur in the blood-brain barrier in addition to the periphery.[42, 85] Animal studies have found no difference in ASM plasma concentrations between responders and nonresponders overall, though these experiments have used intraperitoneal rather than oral administration.[38, 86]

6.4.Intrinsic Severity Hypothesis

The concept is that ASM resistance does not depend on specific pharmacoresistant factors but rather on neurobiological factors underlying severity. More difficult epilepsies are more challenging to treat as a concept has been proposed.[87] The intrinsic severity theorizes that greater disease strength, as represented primarily by high early seizure frequency, will likely translate to greater drug resistance.[88] Rodent models of basolateral amygdala stimulation have indicated that epileptic rats responding to treatment exhibited low, uniform seizure frequency, while many nonresponders had high seizure frequency. Some nonresponders showed low seizure frequencies, similar to responders.[89] Similarly, some high seizure frequency individuals may become responders.[90] Accordingly, the main criticism of this model is that while high seizure frequency is a strong predictor of pharmacoresistant, other predictors exist.[38] It was also suggested that other measures of epilepsy severity, including the extent of structural lesions or behavioural phenotype, predicted ASM resistance.[88] Improved understanding of the pathophysiology of epilepsy may allow improved forecasting of pharmacoresistant based on intrinsic severity.[72]

6.5.Neural Network Hypothesis

The neural network hypothesis indicates that constant excitatory stimulation during seizures leads to neurodegeneration, synaptic reorganization, necrosis, gliosis, and axonal sprouting, resulting in an abnormal network reducing ASM efficacy.[91] Circumstantial clinical

evidence supporting this hypothesis is that malformations in cortical development are often associated with drug resistance,[92, 93] while surgical management of structural lesions can promote seizure freedom. Approximately 60% of people with previously drug-resistant TLE are seizure-free with continued medical treatment following temporal lobe resection.[94] In rodent models, >90% of nonresponders to ASMs had a significant loss of neurons in the CA1, CA3c/CA4, and dentate hilus. In comparison,>90% responders did not differ in hippocampal morphology from nonepileptic controls, demonstrating the role of functional alterations in hippocampal pyramidal neurons and the dentate gyrus secondary to hilar cell loss in pharmacoresistance.[38, 95, 96] Astrocytes have been implicated in pathological processes, including regulation of excitatory synapses of abnormal networks and forming glial scars that prevent axon growth in damaged regions and blocks an ASM from reaching targets.[63, 97, 98] A complicating factor to this hypothesis is that neural network alterations do not always lead to DRE.[42] Additionally, not all drug-resistant people become responsive to ASMs following epilepsy surgery, though incomplete resection of affected tissue may partly explain this finding.[42, 63, 99] Existing data appear to support this hypothesis in defining the role of hippocampal sclerosis in pharmacoresistant TLE.

6.6.Gene Variant Hypothesis

The gene variant hypothesis suggests that an epileptic phenotype is generated by mutations or polymorphisms in genes encoding enzymes, receptors, ion channels, and other components.[100] Studies examining CYP2C9 across ethnicities have shown that polymorphisms may lower phenytoin metabolism and increase the risk of concentration-dependent toxicity.[101, 102] The metabolism of other ASMs, including valproic acid, carbamazepine, oxcarbazepine, and lamotrigine, are affected by genetic variations in genes. These variations are responsible for synthesising enzymes, ion channels, and receptors involved in maintaining normal brain electrical activity.[38, 103, 104] Alterations in these genes may promote abnormal conductance and ASM resistance, leading to DRE.[38] At present, despite myriad genome-wide association studies and corresponding meta-analyses, there have been no generally accepted genetic associations for drug resistance across epilepsies to support broad, syndrome-independent, genetically driven mechanisms of DRE.[38] Challenges to this hypothesis are weak evidence, small sample sizes,

differing clinical groups and definitions, examination of only a select number of mutations or polymorphisms, and methodological issues and inability to replicate existing studies.[38, 100, 105]

6.7.*Epigenetic Hypothesis*

The epigenome, the set of molecules regulating gene expression throughout the genome, has been implicated in DRE.[38] Investigating the epigenomic role in drug resistance is likely to be challenging. An existing study has associated specific microRNAs with human TLE, but the source tissue was resected from people with DRE, rendering it difficult to determine cause and effect.[38, 106, 107] While much of the remaining evidence, arising from animal models, indicates that manipulation of specific microRNAs may influence epilepsy, studies often have study design shortcomings, and numerous knowledge gaps remain.[38, 108-110] It is also largely unknown whether this extends to humans and its role in pharmacoresistance.[38] A pilot study comparing 27 people with epilepsy with 20 age- and sex-matched controls has determined that microRNAs 142 and 224 are suitable for distinguishing drug-sensitive from drug-resistant TLE.[111]

6.8.Gut Microbiome Hypothesis

The gut microbiome has recently attracted interest for its potential role in epilepsy. Gut dysbiosis is associated with inflammation, blood-brain barrier disruption, and altered neuromodulatory activity.[112, 113] The gut microbial community of people with DRE seems substantially dissimilar from those with drug-sensitive epilepsy, with an abnormal increase in the abundance of rare flora. In contrast, gut microbiome composition was similar between people with drug-sensitive epilepsy and controls.[114] People with DRE have a relative abundance of *Firmicutes (Negaticutes)* and deficiency of *Bacteroides finegoldii* and *Ruminococcus_g2*.[115] The Bacteroides/Firmicutes ratio has been postulated as an essential determinant, such that ciprofloxacin therapy may increase the ratio and decreases seizure frequency.[116] A pilot study has demonstrated the efficacy of probiotics in reducing seizure frequency and improving quality of life.[117] Further investigation is necessary into the role of the gut microbiome in DRE.

6.9.*Neuroinflammation*

Neuroinflammation has been implicated in DRE through three primary mechanisms. The first is the destruction of tight contacts between endothelial cells, induction of abnormal

angiogenesis, and oxidative stress, promoting seizure.[118, 119] Similarly, artificially induced dysfunction of the blood-brain barrier leads to developing epileptic foci in previously healthy brains.[118] Inflammatory activity of astrocytes may compromise the integrity of the blood-brain barrier, creating a cycle that promotes seizure recurrence and cell loss.[119] Neuroinflammatory processes may promote generation of aberrant connections between neurons, catalyzing defective or hyperexcitable neural networks.[119] Accumulation of serum albumin, which is not usually present, further promotes seizures. A study examining acute rat entorhinal cortex-hippocampal slices demonstrated that phenytoin and carbamazepine do not suppress seizure-like events precipitated by 4-aminopyridine when albumin perfuses tissue.[120] Presumably, this results from ASM binding to albumin.[119] Release of inflammatory mediators and glutamate by astrocytes and neurons due to brain injury or recurrent seizures may increase multidrug transporters. This would include P-glycoprotein and its pro-inflammatory mediators in the blood-brain barrier, leading to pharmacoresistance, much like the transporter hypothesis.[38, 119, 121] For example, cyclooxygenase-2 (COX-2) and interleukin-1B (IL-1B) upregulate P-glycoprotein production.[38] Voltage-dependent ion channels may undergo post-translational modification by inflammatory mediators, reducing sensitivity to ASMs.[119, 122] Additional work is needed to delineate the role of neuroinflammation in DRE in full.

7. Verifying Drug Resistance

In determining whether an individual has DRE, it is crucial to verify that the medication and administration specifics are appropriate and rule out treatment nonadherence.

7.1.Pseudoresistance

Pseudoresistance is a concern in the management of epilepsy. The diagnosis must be accurate for the individual. Second, medication must be reviewed.[14] If ASMs are unsuitably for their specific epilepsy type, doses are too small, the interval between doses is too long, or the ASM has not been used for a sufficient time. The person may not have pharmacoresistance to a given ASM.[14] Adjustments to the medication regimen should be accordingly made.[14] Additionally, inquiries into factors affecting ASM metabolisms, such as alcohol and drug abuse, must be made.[14]

7.2.Adherence

Compliance is a one-way relationship with a medical provider, in which the clinician dictates the medication regimen, and the recipient is expected to comply. In contrast, adherence involves a therapeutic rapport between the clinician and the individual.[123] The terms are often used interchangeably, but adherence is a more valuable conceptualization. The prevalence of significant medication nonadherence in people with epilepsy varies between 26% and 79%.[124] Table 1 provides a summary of risk factors for poor adherence.[125-133] Nonadherence increases seizure risk and may lead to pseudo-refractory epilepsy.[134]

Direct means for assessing adherence include plasma or serum ASM levels, saliva concentration, or detection on human hair.[135] Evaluation of serum or plasma ASM levels, done at least twice, is the most commonly used measure.[135] A drop in medication level of a certain percentage, dependent on the ASM, represents nonadherence.[135] Evaluating serum levels is often variable based on individual-specific factors, including age, food intake, drug interactions, and ASM used.[136] While measurement effectively assesses intake in low adherence situations; it may not be accurate enough to optimize treatment, particularly monotherapy.[137] Additionally, saliva sampling yields similar results to serum or plasma monitoring. It has the advantage of being the least painful method and is useful for pediatric or geriatric patients with poor venous calibre.[138-141] Saliva sampling is limited by the need to reference saliva concentrations to baseline saliva production for the individual and variability in serum to saliva ASM ratios.[135, 138] Similarly, saliva sampling may be arduous in settings with large throughput because its greatest efficacy arises from reference to the individual.[135] Hair sampling is an alternative. Some believe that the utilization of hair samples is not sufficient for determining ASM concentrations. In contrast, others have found similar sensitivity to blood plasma results or greater accuracy than blood plasma or self-report methods.[142-144] Hair levels of ASMs may not always correspond to clinical outcomes.[145]

Indirect means for assessing adherence include self-report measures, pill counts, appointment attendance, medication refills, and seizure frequency.[135] Self-report measures are low cost, noninvasive, and easily adaptable but vary in development, validation, and implementation.[135] Few measures have been validated specifically for medication adherence in epilepsy.[135] The QOLIE-AD-48, designed to measure health-related quality of life for adolescents with epilepsy, is sometimes used.[146] The Medication Adherence Report Scale has

been applied to people with epilepsy.[147] The Morisky scale, initially developed for hypertension, has been validated for adherence in epilepsy.[148, 149] An array of scales to determine ASM adherence and analyze the ability of people with epilepsy to manage their conditions in other areas has also been developed.[150-153] Other general questionnaires may include questions on adherence. Given that self-report measures are inherently subjective, individual misperception or social desirability bias may lead to over-reporting of adherence.[154, 155] Pill counts are noninvasive and easily tampered with.[135] Event recorders can be integrated into pill bottles to measure the number of bottle openings. They are more accurate than pill counts or serum concentrations, but they may overestimate adherence given a bottle opening does not mean that the ASM has been taken.[135, 156] Appointment attendance is easily determined from records and may indicate general adherence to treatment but does not necessarily translate to medication adherence over time.[135] Medication refills are useful in managed care settings and may correlate with ASM blood levels but do not account for online pharmacies.[135, 157, 158] Measuring seizure frequency over time is rarely used because seizure frequency may not correlate with medication intake.[135] Importantly, none of the indirect methods provide proof that ASMs are taken.[135]

Strategies for assessing adherence are unstandardized, and utilizing a singular direct or indirect measure alone is insufficient. One study found that a combined approach using the Morisky scale and pill count was more effective than using either tool alone.[159] Better systems to assess adherence are needed. A composite system consisting of direct and indirect measures for compliance is optimal. One suggestion is to develop a validated clinical prediction rule incorporating blood or plasma concentrations of ASMs, the Dilorio or Morisky scale, and appointment attendance. Querying challenges may uncover issues affecting adherence. Strategies must be developed to increase ASM adherence. Educational measures have shown reasonable success but should be used in a structured manner.[160, 161] Educational interviews with a pharmacist may be instrumental in improving adherence.[162] Behavioral interventions, such as intensive reminders and implementation involving an “if, then” plan, enhanced adherence to a greater degree.[160] A study combining oral education, written materials, and monthly calls with a pharmacist with a modified medication schedule showed that adding the medication schedule, a behavioural intervention, did not improve adherence.[163] Combining motivational interviewing with a calendar to self-monitor adherence and measures to involve family members improved medication adherence.[147] Comprehensive interventions may incorporate multimodal education

via oral communication, videos, written materials; motivational interviewing; a medication schedule; and close follow-up from a pharmacist and seek to engage families or caregivers.

7.3.Socioeconomic Considerations

Healthcare usage and expenditures are high in people with DRE, such that the total cost of treating per person is $138,600 per year compared to $4,272 for effectively treated people.[164, 165] Nonadherence rates may be as high as 55% in adults with epilepsy despite positive beliefs regarding the efficacy of ASMs, indicating that socioeconomic factors play a role.[166, 167] Per-capita income, ASM availability, and costs are associated with nonadherence, as are lower educational status and unemployment.[124, 131, 166, 168] Related to socioeconomic status, knowledge regarding the benefits of ASMs is essential. Better informed individuals have increased rates of ASM adherence than those who are poorly informed.[169] Health literacy is a protective factor against nonadherence by improving the perception of the need to intake ASMs.[166] Importantly, measures to improve adherence should incorporate socioeconomic considerations in addition to standard demographic, epilepsy status, and clinical variables.

8. Principles of Epilepsy Treatment

Epilepsy treatment focuses on maximizing quality of life and function while minimizing the potential adverse effects of seizures and treatments. The core principles of epilepsy treatment have been unchanged over the last three decades. It is essential to emphasize the need to tailor these principles to people with DRE.

8.1.*Individual Perspectives*

Seizure freedom is often the primary goal of treatments. Still, individuals may emphasise other aspects of daily functioning such as sensorimotor function, cognitive status, neuropsychological functioning, sleep, and lifestyle factors.[170] People often value independence and living without fear or anxiety.[170] An approach to the care of a person with epilepsy involves maximizing the opportunity for seizure freedom while centring individuals' perspectives.

8.2.Informational Needs

Another principle is satisfying the informational needs of people with epilepsy and their caregivers. Core informational needs are general information, ASMs, seizure triggers, first aid guidelines, lifestyle, possible psychosocial consequences, and women-specific issues such as contraception and pregnancy.[171] Proper communication strategies, including simplifying language, avoiding jargon, emphasizing important information, incorporating baseline health literacy and needs into explanations, assessing understanding, and filling knowledge gaps or correcting misconceptions are essential.[172, 173] Multimodal educational interventions may be particularly useful.[172, 173]

8.3.Treatment

One principle is selecting an appropriate treatment. First and foremost, the diagnosis must be firmly established before beginning treatment.[174] Once the type of epilepsy has been determined, ASMs are selected based on efficacy, then tolerability, drug interaction profile, and ease of use.[174, 175] ASM choice should be tailored to the individual including age, sex, and learning disability; epilepsy syndrome; seizure types; lifestyle issues; and cotreatments based on the best available evidence.[171, 174] Awareness of the pharmacological profile of the ASM may optimize benefit while minimizing adverse events.[170] The ASM may be replaced with another ASM if the individual is unresponsive or experiences bothersome adverse effects. People who do not respond adequately to monotherapy should be managed with appropriately selected combination therapy.[171] Those with focal epilepsy who do not achieve adequate seizure control with ASMs, particularly those with lesions with concordant clinical features, may be referred for evaluation for surgery. If this is not appropriate, neuromodulatory approaches such as vagal nerve stimulation, responsive neurostimulation, or deep brain stimulation may be considered.[171, 176-179] The diagnosis, knowledge regarding epilepsy and the treatment, and treatment adherence should be reviewed prior to changing or escalating treatment.

8.4.Active Follow-up

An additional principle is an effective follow-up. Individual management and education is a longitudinal process.[180] People should be reviewed at least yearly.[171] At each review, pharmacological aspects, including evaluation of the effectiveness of ASMs and adverse effects, effect of comorbidities, and use of cotreatments such as anticoagulants or oral contraceptives

pills, should be addressed. Non-pharmacological aspects, such as general safety advice, driving regulations, reasonable expectations and limitations, and practical and social support sources, should also be addressed.[171]

9. Newly Approved Anti-seizure Medications

Investigation regarding other ASMs that may decrease rates of DRE is underway. These ASMs may promote seizure freedom through mechanisms or formulations that are different than those of the standard ASMs. Only one ASM (cenobamate) has been approved in the last five years, along with three orphan drugs that have shown efficacy for specific epilepsy syndromes.

9.1.*Cenobomate*

Cenobomate, a novel tetrazole alkyl carbamate derivative, was approved by the United States Food and Drug Administration for focal epilepsy in adults in November 2019.[181] The decision was based on two randomized controlled trials and a large multicenter, open-label, safety study.[182-184] Cenobamate resulted in significant reductions in seizure frequency across all focal seizure types. There were also higher seizure freedom rates than those randomized to receive a placebo.[182-184] A subsequent meta-analysis reaffirmed the significant improvements in seizure freedom rate with adjunctive cenobamate, as well as a higher rate of adverse events, compared with placebo.[185] A pooled analysis of the two randomized trials and safety study found cenobamate retention rates of 80% at one year and 72% at two years, with adverse events as the most common reasons for discontinuation.[186] This ASM appears to block persistent Na+ currents and enhance GABA-mediated inhibition of positive allosteric modulation of the $GABA^A$ receptor by acting at a non-benzodiazepine-sensitive binding site.[187, 188] Cenobamate may serve as an alternative to other ASMs to reduce DRE rates.

9.2.Fenfluramine

Fenfluramine (3-trifluoromethyl-*N*-ethylamphetamine) was initially launched as an appetite suppressant. Fenfluramine is a serotonin-releasing agent, and its major active metabolite, norfenfluramine, binds to and activates 5-hydroxytryptamine receptors 2B and 2C with high affinity and 2A with moderate affinity.[189] Two randomized controlled trials have have shown that fenfluramine decreased convulsive seizures in children with Dravet syndrome as add-on

therapy relative to placebo and was well-tolerated.[190, 191] One of these studies found improved quality of life in children on fenfluramine relative to placebo.[191] A small pilot study in children with Lennox-Gastaut syndrome also showed >50% reduction in convulsive seizures in the majority of participants.[192] Across these studies, most adverse effects were minor, but hospital admission due to status epilepticus was the most common serious adverse event.[190-192] Large multi-centre international studies are pending. If results are favorable, fenfluramine may be utilized for people with Dravet syndrome or Lennox-Gastaut syndrome, two conditions with high levels of DRE.

9.3.Cannabidiol (Epidiolex ®)

Epidiolex ®, a cannabinoid containing greater than 99% cannabidiol (CBD) and less than 0.1% of Δ9-THC, is the first cannabinoid medication approved by the Food and Drug Administration for Dravet syndrome and Lennox-Gastaut syndrome.[193] The first open-label study of CBD focused on 162 individuals aged 1-30 years with childhood-onset epilepsy treated with CBD over 12 weeks at 11 US centres.[194] Oral CBD lead to a mean reduction of monthly motor seizures at 36.5% and nearly 50% reduction in median monthly convulsive and total seizures at 12 weeks, with similar improvements during the 96-week follow-up period.[194] Additionally, four large randomized controlled trials in people with Dravet syndrome and Lennox-Gastaut syndrome have provided further evidence regarding the efficacy of Epidiolex, demonstrating significant reductions in total seizures, monthly convulsive seizure frequency, and monthly drop seizure frequency relative to controls.[195-198] Somnolence, decreased appetite, diarrhea, prexia, fatigue, and vomiting were the most common adverse effects.[195-198] The differences in drop seizure reduction between CBD and placebo became significant at day 6 for people with Lennox-Gastaut syndrome and day 12 for people with Dravet syndrome.[199, 200] Most adverse events resolved within the 14-week study period.[199, 200] An additional study indicated that greater anti-seizure effects were obtained when CBD was combined with clobazam in people with Lennox-Gastaut syndrome.[201] Studies investigating the efficacy of Epidiolex ® for focal epilepsy are underway. If optimistic, these studies may indicate a role for Epidiolex ® in minimizing DRE for people with focal epilepsy.

9.4.Everolimus

Everolimus is an inhibitor of the protein kinase mammalian target of rapamycin (mTOR) and is used for intractable seizures in people with tuberous sclerosis complex.[202] The first open-label phase I/II clinical trial reported reductions in seizure frequency ≥50% in 80% of people with TSC, and seizures were reduced in 85% of people with a median reduction of 73%.[203] Quality of life and parent-reported behaviour improved.[203] A long-term follow-up study reported 13 of 14 participants had ≥ reductions in seizure frequency at 48 months.[204] All participants reported an adverse event, of which 94% were mild or moderate.[204] Improvements in quality of life and parent-reported behaviour were not statistically significant.[204] A phase 3 randomized, double-blinded, placebo-controlled trial reported reductions in seizure frequency of 39.6% in the high-exposure everolimus group and 29.3% in the low-exposure group relative to 14.9% to placebo, while serious adverse events occurred in 14% of the low-exposure and high-exposure groups.[205] The utility of everolimus for tuberous sclerosis is dubious, as at least half of people with tuberous sclerosis complex do not show clinically meaningful decreases in seizure frequency.[206] Additional studies examining the role of everolimus in decreasing the prevalence DRE among people with tuberous sclerosis are necessary.

10. Conclusion

DRE is a challenging subset of the spectrum of epilepsies. Clinical factors predictive of DRE have been identified, but mechanisms of DRE require further investigation. Appropriately managing people with DRE requires utilizing the principles of epilepsy treatment as a foundation and considering the impact of pseudoresistance and nonadherence, along with corresponding socioeconomic considerations. Cenobamate holds promise for DRE, but new ASMs are still needed to conquer DRE fully.

Declarations

Funding: Nathan A. Shlobin received no funding. Josemir W. Sander is based at the NIHR University College London Hospitals Biomedical Research Centre, which receives a proportion of funding from the UK Department of Health's Research Centres funding scheme. He receives research support from the Dr Marvin Weil Epilepsy Research Fund, from the UK Epilepsy

Society and the Christelijke Vereniging voor de Verpleging van Lijders aan Epilepsie, Netherlands.

Conflicts of interest / competing interests: Nathan A. Shlobin has no disclosures to report. Josemir W. Sander reports personal fees from Eisai, UCB, GW, Arvelle and Zogenix, grants from UCB outside the submitted work.

Ethics approval: Not required or sought. This was a narrative review of existing literature.

Consent to participate: Not applicable.

Consent for publication: Not applicable.

Availability of data and material: All relevant data can be found in the references of this review.

Code availability: Not applicable.

Authors' contributions: Nathan A. Shlobin conducted the literature search and data analysis and drafted the manuscript. Josemir W. Sander formulated the concept for the article and provided critical intellectual input to the work. Both authors have read and approved the final submitted manuscript and agree to be accountable for the work.

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