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Pharmacotherapeutic strategies for drug-resistant epilepsy in children

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ABSTRACT

Drug resistance is defined as the failure of adequate trials of two tolerated and appropriately chosen antiseizure medications to achieve sustained seizure freedom. In case of uncontrolled seizures, pseudo-drug-resistance (poor compliance, a worsening effect of an antiseizure medication, a diagnosis of psychogenic non-epileptic seizure) should be first ruled out in case of pediatric epilepsies. This paper discusses the process of choosing antiseizure medication and the concepts of rationale polytherapy and precision medicine. In drug-resistant epilepsy, when curative surgery is not feasible, the aim of the treatment is focused on the improvement of quality of life rather than on seizure count. In recent years, despite an increase in available antiseizure medications, the incidence of drug-resistant epilepsy has not changed. Precision medicine may offer in rare epilepsies a mechanism-driven treatment, but it is still unclear if this will end up in an improvement of efficacy in drug-resistant epilepsies. Gene therapy with antisense oligonucleotides or Adeno-associated Virus (AAV) is transitioning from the experimental side to the first human trial. It may modify the natural history of selected epileptic syndromes.

1. Introduction

Among epilepsy patients, the persistence of seizure recurrence despite appropriate use of antiseizure medications (ASM) is not uncommon because 20–30 % of patients with epilepsy are drug-resistant [1]. Several definitions of drug-resistant epilepsy have been used until the formal definition from the International League Against Epilepsy (ILAE), which was published more than ten years ago: 'Drug-resistant epilepsy (DRE) may be defined as failure of adequate trials of two tolerated and appropriately chosen and used ASM schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom [1].

Pediatric cohort studies have identified risk factors for developing DRE, such as a history of neonatal seizure, a high number of seizures at epilepsy onset, an identified underlying cause, the co-occurrence of intellectual disability, an abnormal neurological exam, or an abnormal neuroimaging [2]. DRE is associated with a decrease in quality of life, as well as an increase in risk for injuries, status epilepticus, comorbidities, and sudden unexpected death [3]. The parental quality of life is also affected by having a child with DRE. The quality of life is more affected in epilepsy than in other chronic health conditions [4]. A prospective cohort study on 613 children examined the timeline for new-onset epilepsy to progress to drug-resistant. In this cohort, 142 (23.2 %) met the ILAE definition for DRE; 39 out of 142 (27.5 %) met the criteria for DRE three years following the initial diagnosis [5]. These findings underscore the need for continuous re-evaluation of patients to ensure timely diagnosis of DRE.

When good seizure control is not achieved with ASM, other therapeutic options should be considered, such as epilepsy surgery, dietary treatment, or neurostimulation. First, it is crucial to identify if the patient could be a surgical candidate. Resective surgery may offer sustained seizure freedom with an improvement of the quality of life [6] and, if performed early in life, may protect from cognitive decline associated with high seizure burden [7]. If resective surgery is not achievable, dietary treatment, palliative surgery, or repetitive neurostimulation systems (including vagus nerve stimulation) could be discussed individually, taking into account the age of the patients, the epilepsy syndrome, and the individual benefit-risk ratio [8,9]. Furthermore, prioritizing precision medicine to target underlying mechanisms for improved efficacy is essential, particularly in monogenic epilepsy

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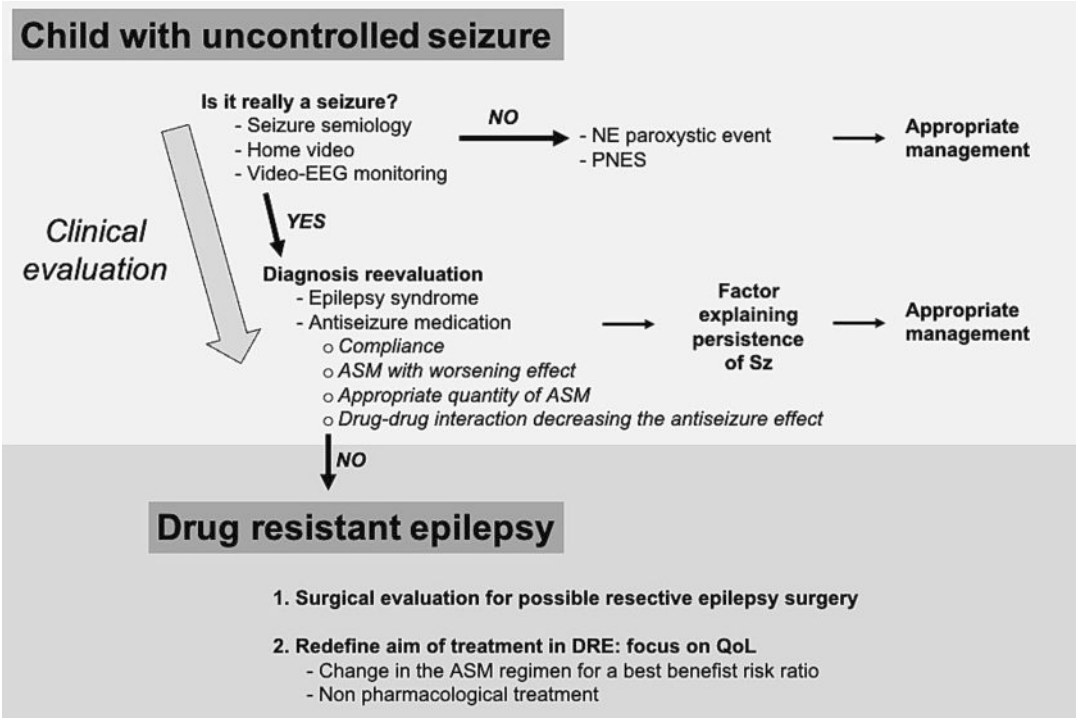

Fig. 1. Overview of the evaluation of a child with uncontrolled seizure. There are two steps. First, rule out non-epileptic events and pseudo- drug-resistance. Second, redefine the aim of treatment and manage the treatment of drug-resistant epilepsy, focusing on the quality of life.

with treatments that act on seizure pathways or in immune-related epilepsies with immunomodulation approaches.

This paper aims to outline pharmacotherapeutic strategies for managing DRE in patients not candidates for surgery. We conducted an unstructured literature review approach based on the two authors' knowledge to select the most relevant topics, ensuring a comprehensive discussion of key issues. Based on the ILAE definition of DRE, we discuss the decision process for choosing which ASM to add and how to combine them. We also discuss the new ASMs and the concept of precision medicine for epilepsies.

2. ILAE definition of Drug-Resistant Epilepsy: Implications for treatment management

As mentioned above, the ILAE defined a DRE as a failure of adequate trials of two tolerated and appropriately chosen and used ASM schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom [1]. This definition is based on the fact that seizure freedom is achieved mainly by the first two drug trials, and the probability of seizure freedom with a third ASM is very low, moving from 8 % with the third ASM to 2.5 % after the fifth ASM [1,10]. Observational cohorts of newly diagnosed epilepsy have established this in both adults and children. In the Dutch pediatric epilepsy cohort, 46 % on one ASM, 19 % on a second ASM, and 9 % on all additional ASM regimes achieved at least a 1-year seizure-free period over this 5-year study [11]. Similar findings were observed in the Nova Scotia Cohort: of 417 children with epilepsy, 83 % became seizure-free with a single ASM. Of the 72 who did not respond to the first ASM, 30 (42 %) became controlled at the end of follow-up (92 ± 26 months) [12].

In addition to providing a common language for the community, the ILAE definition reminds us that the absence of response to ASM is not synonymous with a DRE. Indeed, the use of inappropriate ASM, suboptimal doses of ASM, and poor compliance could explain the absence of seizure freedom.

However, certain aspects of the DRE definition should be revisited to encourage new research and prevent treatment delays [13]. Some structural abnormalities, such as megalencephaly or, to some extent, focal cortical dysplasia, are unlikely to respond to any medication and could be considered DRE from the first seizure associated with these etiologies. Similarly, certain genetic etiologies, such as pathogenic variants in SCN1A predictive of Dravet syndrome, may indicate a poor response to treatment as early as the first status epilepticus [14].

Evaluating a child with persistent seizures requires a systematic, step-by-step, checklist-based approach to ensure that no option is overlooked. Fig. 1 can serve as a helpful checklist to guide this assessment process.

The absence of response to the ASM is not always due to drug resistance (Fig. 1). This may be related to non-adherence of the patients to the ASM, the occurrence of non-epileptic events such as psychogenic non-epileptic seizure (PNES) [15], a pharmacologic interaction resulting in a decrease of the efficacy of the ASM regimen, or the use of an inappropriate ASM. Regarding compliance, this issue should be addressed very early in the disease course because it has been shown that early poor compliance is related to lower long-term seizure control [16]. In a prospective study including 124 children (2–12 years of age), the children with initial nonadherence to ASM were 3.2 times more likely not to achieve ≥ 1 year of seizure freedom if compared with children with good adherence ($p = 0.02$) [16]. The non-adherence is frequent. Metanalyses found pooled non-adherence in children between 27 % and 42 % [17]. Adherence barriers in children are different according to age. This includes difficulties in swallowing medications, forgetfulness, and infants or young children refusing or spitting out ASM [18]. In addition to the non-adherence assessment, the seizure semiology should also be carefully evaluated to exclude PNES that could be mistaken for DRE. The use of smartphone video could be beneficial in such cases, as demonstrated recently in a class II study, which showed the accuracy of smartphone video in diagnosing epileptic seizures and PNES [19]. Video-EEG recording of the event remains the gold standard when there are doubts about the diagnosis [20].

Drug-drug interaction and the worsening effect of ASM that could also lead to uncontrolled seizures are discussed below. A cross-sectional retrospective study investigated the causes of uncontrolled seizure and

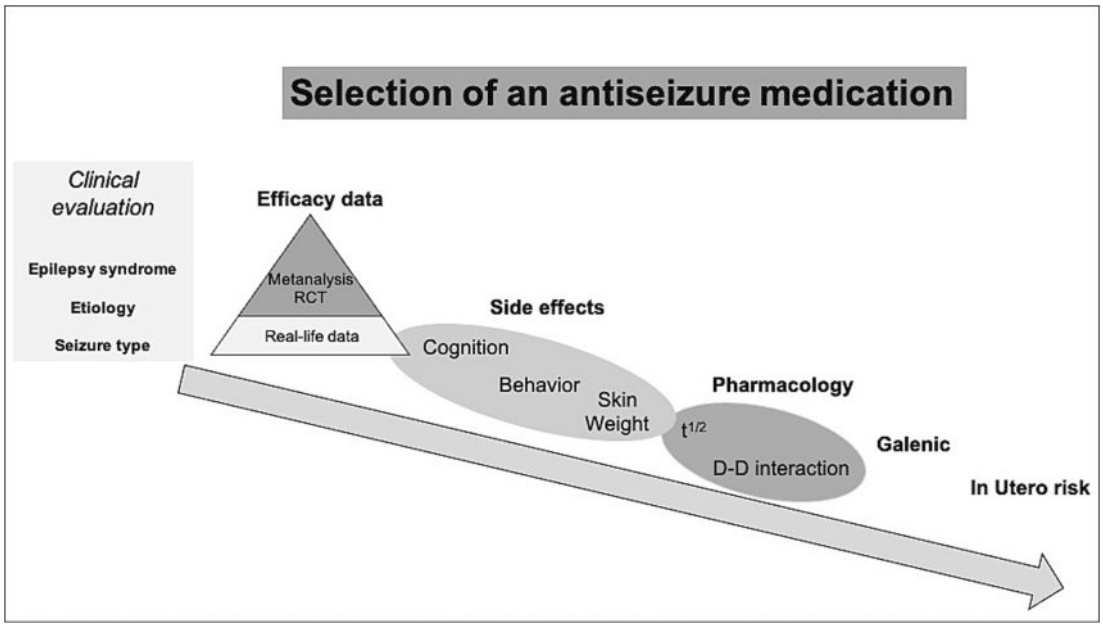

Fig. 2. Overview of the factors to be considered for the prescription of an antiseizure medication.

pseudo- drug-resistance to ASM. Among 198 children with uncontrolled seizures, 4 % did not have epilepsy. Overall, 47 % of children with uncontrolled seizures had DRE, 37 % were taking inappropriate ASMs, 10 % were under suboptimal doses, and 2 % were considered to have poor adherence to treatment [21].

3. Choose the antiseizure medications to combine for a child with drug-resistant epilepsy

3.1. Choose an antiseizure medication

The treatment of pediatric epilepsy is individualized. Monotherapy should be first tried. Since most patients would be seizure-free under monotherapy, this remains the treatment of choice for newly diagnosed epilepsy. If the first monotherapy is not effective, a second monotherapy is suggested. This minimizes the risk of side effects. After the failure of two monotherapies, a combination of two ASMs is considered.

The first important step is to select an ASM according to the seizure type or the epilepsy syndrome. Most evidence on the efficacy of ASM comes from randomized clinical trials (RCT) evaluating each new compound versus placebo, resulting in a lack of evidence that any ASM is more effective than others except in the case of childhood absence epilepsy first-line treatment [22]. Multicenter, unblinded RCTs evaluating the effectiveness and cost-effectiveness of various antiseizure medications (ASMs), like SANAD studies conducted in adults, have yielded important insights into the superior efficacy of certain ASMs over others [23–26]. The ASM is then chosen based on an individual basis. The seizure type and the epilepsy syndrome are the major players in the choice of an appropriate ASM (i.e., choose first an ASM with demonstrated/possible efficacy and avoid ASM with worsening effect). In the second stage, the side effect profile of the ASM, the gender, the age, pharmacological characteristics of the ASM, and the available formulation of the drug are also points to take into consideration (Fig. 2).

Regarding the side effect profile, a particular focus on cognition and behavior is crucial during childhood. Many reports have described the possible cognitive effects of ASMs, even if studies on the cognitive effects of ASMs are lacking in terms of quantity and quality [27]. Unfortunately, current drug development uses only screening tools for the negative impact of ASM on cognition and behavior. Therefore, subtle changes and long-term exposure effects are not identified. Monotherapy should be prioritized over polytherapy to minimize the risk of cognitive side effects [28].

Moreover, a higher number of concomitant ASMs is also associated with a higher risk of cognitive impairment. Indeed, there is a different effect of the burden of ASMs on seizures and side effects. When the quantity of ASMs increases, the effect on seizures reaches a plateau, while the risk of side effects is exponential [27]. Similarly, psychiatric conditions increase the risk for behavior difficulties with ASM associated with this kind of side effect (levetiracetam, perampanel, phenobarbital) [29]. Cognition and behavior should always be carefully monitored using ASM, particularly with polytherapy [29].

Clinical history should be evaluated when selecting an ASM. Any history of skin reactions related to previous use of an ASM should be asked, as this can significantly increase the risk of another rash [30,31]. The cross-sensitivity rates between ASMs could be very high, particularly with carbamazepine and phenytoin [31].

Gender should also be taken into consideration to avoid the prescription of ASMs in female adolescents with potential teratogenic effects. If the patient becomes seizure-free with a given ASM, it is most likely that the same monotherapy will be maintained until the childbearing potential age. Therefore, careful consideration should be given at the time of the first ASM prescription. In utero, exposure to ASM could be responsible for an increased risk of malformation and developmental consequences (cognition and behavior) [32–35]. It is better to initiate the first ASM with a safer profile (lamotrigine or levetiracetam). Whilst valproate and topiramate are currently at the forefront of concern over teratogenic risks, it is essential to keep in mind that the most recently approved ASM should still be used with caution. The absence of data does not mean that there is no risk. The absence of data does not mean that there is no risk. Moreover, valproate is sometimes the best option to achieve seizure control, e.g., in Idiopathic Generalized Epilepsies [36,37].

Some ASMs are enzyme-inducers. They could be responsible for a clearance increase of co-administered drugs, resulting in a shorter half-life of a concomitant ASM. This phenomenon increases the fluctuation of the ASM serum concentration; as a consequence, patients may experience higher peak blood levels and lower mean blood levels with the related risk of toxicity or seizure recurrence [38]. In patients with polytherapy, this should be kept in mind to avoid enzyme inducers or

measure ASM serum levels in case of inadequate seizure control. This could also be a concern for the use of enzyme-inducer ASMs in female adolescents as it could be a concern for the use of estroprogestative contraception [38]. Clinicians must know the pharmacokinetic characteristics and side effects of ASMs before any prescription.

3.2. Combined antiseizure medications

With the current available ASMs, there are more than one hundred possible bitherapies and more than one thousand combinations of three or more ASMs. Without any guidelines, the combination of ASMs is mainly based on a theoretical rationale. The concept of "rational polytherapy" consisting of the combinations of ASMs with different mechanisms of action, has been developed to increase the efficacy by some synergistic effects. However, the gain of the efficacy on seizure frequency remains controversial [39]. There is no evidence for synergistic interaction between ASMs except for the co-medication with valproate and lamotrigine [40–42], as well as the biotherapy stiripentol and clobazam in Dravet syndrome [43,44]. The concept of rational polytherapy should be carefully considered from a safety point of view, as the combination of ASMs with a similar mechanism of action definitively increases the risk for side effects. Indeed, the combination of sodium-channel blockers is well known to result in a higher side effect occurrence and premature withdrawal of the ASM. This has been reported in a pooled analysis of clinical trial data for lacosamide [45].

Innovative methods such as network *meta*-analysis tried to provide evidence for the efficacy of an ASM compared to another without conducting a head-to-head comparison in an RCT [46]. Using the data of pediatric RCTs based on a common comparator (placebo or standard of care), treatment effect was assessed after the selection of 46 RCTs representing 5652 individuals randomized to 22 ASMs or placebo [47]. The network analysis for focal onset seizures consisted of five studies for newly diagnosed epilepsy and nine studies for DRE. Perampanel in drug-resistant focal epilepsy (OR=2.5, 95 %CI=1.1-5.8) was more effective if compared with placebo. The same analysis also found that levetiracetam was more effective than placebo (OR=3.3, 95 %CI=1.3-7.6) [47]. Further future validation of innovative methods may help clinicians to combine ASMs with higher efficacy on seizure.

Polytherapies should be used with caution. It has been shown that using 2 concomitant ASMs provided higher efficacy than monotherapy, but using 3 ASMs did not provide any more [42]. However, the rate of behavior and cognitive side effects seem linked to the number of ASMs [29].

4. Is there any benefit in modifying the ASM regimen when two failed?

As mentioned above, the chance of response after 2 ASMs dramatically decreases. After two appropriate and well tolerated ASMs, the goal of the treatment needs to be shifted from seizure freedom to the maintenance of quality of life. This needs to be explained and discussed with parents and patients. The side effects should be minimized, and seizure control is not the ultimate goal. Expectations of seizure control should be based on the specific syndrome, and the etiology should also be considered, which may give more insights into the prognosis at the individual level. The seizure frequency should not remain the main criterion for evaluating the overall effectiveness of ASMs. How seizure occurrence is disrupting daily life should also be taken into consideration: administration of rescue drugs, injuries, admissions to the emergency room, prolonged post-ictal stage, as well as factors such as the psychological impact, cognitive side effects, social consequences, and overall quality of life for the patient and their caregivers.

The decrease in the likelihood of reaching seizure freedom after 2 ASMs failed raises the question of the benefits of trying an additional ASM. In a prospective study of 613 children, 128 did not respond favorably to 2 drugs, and all of them had a trial of at least a third drug.

Table 1
Current overview of precision medicine in the epilepsy field based on preclinical or clinical.

Gene	Syndromes	Candidate drugs	Available preclinical data	Available clinical data
GATOR1 Cx *DEPDC5, NPRL2, NPRL3*	Familial or sporadic epilepsy with FOS+/- MCD +/- cognitive impairement FCD	mTOR inhibitors	rapamycin in Zebrafish [60] rapamycin in DEPDC5 mice [61]	Case series DEPDC5 [62]
GRIN1	DEE Bilateral polymicrogyria	Memantine Radiprodil	In vitro [63]	NCT05818943 ongoing
GRIN2A	EE-SWAS Epilepsy-aphasia	Memantine Radiprodil	In vitro [64]	One patient [65] NCT05818943 ongoing
GRIN2B	DEE	Radiprodil Memantine	In vitro [66] NA	NCT05818943 ongoing Moderate effect in one patient [67]
CHRNA4	SHE	Nicotine	NA	Improvement of 2 patients [68] Case series 17 patients [69]
KCNT1	EIMFS SHE	Quinidine	In vitro [56,70,71]	Varied effect including a phase 2 study [56,71–75]
KCNQ2	SL(F)NE DEE	Retigabine BHV-7000	In vitro [76–78] In vivo [79]	Sodium channel blocker [80,81]
SCN1A	Dravet Syndrome (LOF) GEFS+ (LOF) DEE (GOF)	Bexicaserin (LP352) Clemizole Lorcaserin	Zebrafish – Bexicaserin [82], clemizole and lorcaserin [83] DS Mice [84]	Pacific study NCT05364021 NA NA
SCN2A	DEE EIMFS	Sodium channel blocker	Sodium channel blockers [85] In vitro [86] CaMKII [87]	Sodium channel blockers [81,88,89] (response according to age of onset) [88] Lacosamide in 2 neonates [90] PRAX-562 NCT05818553
SCN8A	DEE	PRAX-562	In vitro [86]	NCT05818553
TSC1, TSC2	IESS FOS	mTOR inhibitors rapamycin everolimus	Mice models treated by rapamycin [51,52,91,92]	Phase 2 and phase 3 RCT for everolimus [53,93]

CaMKII: calcium/calmodulin protein kinase II; Cx: complex; DEE: developmental end epileptic encephalopathy; EE-SWAS: epileptic encephalopathy with spike and wave activation in sleep; EIFMS:; IESS: Infantile Epileptic Spasm Syndrome; FCD: focal cortical dysplasia; FOS: focal onset seizure; GOF: gain NA: not available; MCD: malformation of cortical development; mTOR: mammalian target of rapamycin; SHE: Sleep-related Hypermotor Epilepsy; SL(F)NE: Self-Limited (Familial) Neonatal Epilepsy; RCT, randomized controlled trial;

Seventy-three out of 128 patients (57 %) had a remission. Frequent cycles of remission and relapse were observed. Only 48 (37.5 %) achieved a 1-year remission and 28 (23 %) a 3-year remission [48]. Remission after a second drug failure was common but often transitory. Any remission > one year prior to the second drug failure was not

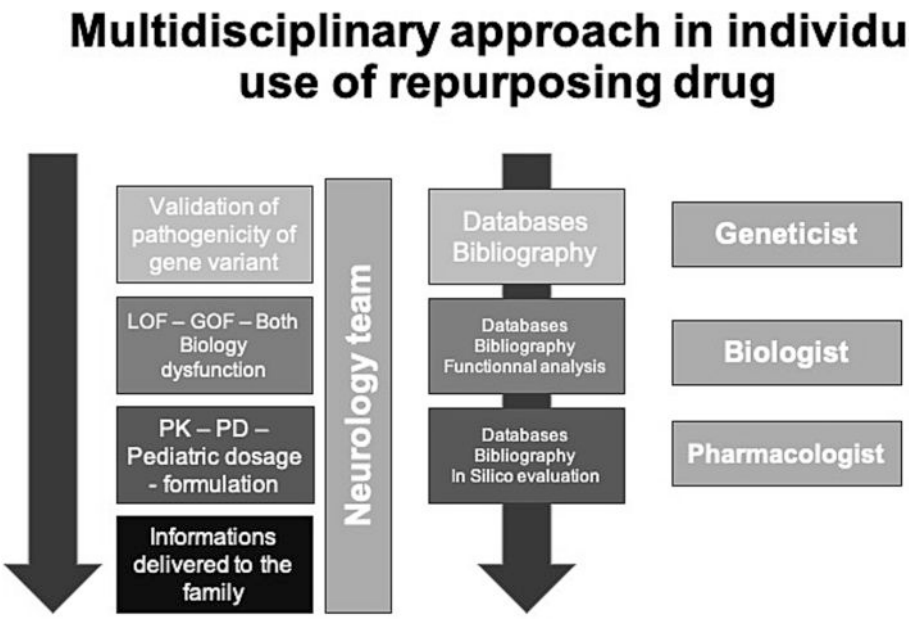

Fig. 3. Overview of the steps for considering the use of a repositioning drug from the identification of a genetic variant in an individual with epilepsy.

predictive of later remission [48]. Children who have not responded to two appropriate drugs should be carefully evaluated to maximize therapy [48]. At the individual level, the change in the ASM regimen could prolong seizure freedom in about 30 % of patients with DRE [49].

5. Precision medicine for epilepsy patients

In the field of medicine, the concept of personalized medicine has emerged as a therapeutic approach based on individual factors to increase efficacy and safety. After a successful development in the cancer field, this approach is now under development in the epilepsy field. Gene sequencing and cloning from patient material allowed rapid expression and identification of dysfunctional proteins (e.g., ion channels) using in vivo or in vitro model systems, which can enable precision in medical treatments in patients by repositioning some compounds approved for other diseases (Table 1). Precision medicine represents a new horizon to control seizures in rare pediatric epilepsies [50]. One example is the positive effect of sodium channel blockers in preclinical studies and children with Gain-of-function *SCN2A*-related epilepsy (Table 1). The development of precision medicine does not focus only on compounds interacting with the ion channels or the neurotransmission. Inhibitors of the mTOR pathways have been tested in various tuberous sclerosis complex (TSC) models, resulting in antiseizure effects and improvement in behavior tests (Table 1). In these rodent models, mTOR inhibitors also improve the histological features [51,52]. This also led to successful drug development with phase 3 randomized controlled trials with everolimus for DRE in TSC patients [53]. However, despite the mechanism-driven repositioning of everolimus, its efficacy was not notably superior. The responder rates observed in the RCTs were comparable to those typically seen in trials for focal-onset seizures in epilepsy [53,54]. Despite promising results, the initial pre-clinical findings do not always fully translate to the clinic. This is similar to recent reports of a lack of efficacy of quinidine in children with *KCNT1* genetic variants [55,56].

The number of hypotheses and the list of compounds have grown quickly in recent years, but they have not been adequately explored (Table 1). When using repurposed compounds for a patient, several key steps are involved: validating the pathogenicity of the gene variants, assessing the biological impact of those pathogenic variants, selecting the appropriate dose and treatment plan based on the compound's pharmacological properties, and providing a clear explanation to the parents (Fig. 3).

In addition, most genetic epilepsies involve haploinsufficiency in a single gene [57]; gene therapy is the next step of treatment, raising the hope of a therapeutic approach improving epilepsy as well as co-occurring neurodevelopmental disorders. There are several ways to target haploinsufficiency in genetic epilepsies: antisense oligonucleotide and viral vector-mediated gene therapy. In the epilepsy field, Dravet syndrome is the first condition targeted for treatment development in humans for both antisense oligonucleotides [58] and the first human administration of targeted AAV [59]. Gene therapies probably represent the ultimate personal medicine, but we don't know if this will result in a cure or a dramatic change in the syndrome phenotypes.

6. Conclusion

The management of DRE in pediatric patients remains a significant and complex challenge. Despite the appropriate use of ASMs, a substantial proportion of patients do not achieve sustained seizure freedom, highlighting the need for a multi-faceted and individualized approach. The persistence of seizures despite ASM treatment necessitates the exploration of alternative therapeutic options early in the disease course. Children with uncontrolled seizures after adequate trials of two or three ASMs should be evaluated at a comprehensive epilepsy center where a strategic re-evaluation of all levels of care can be undertaken, potentially guiding treatment towards alternatives beyond surgical options. This is based on a complete diagnosis assessment should be done again based on careful history-taking and deep examinations such as Video-EEG and brain MRI. The seizure type(s), the epilepsy syndrome, and the review of all tried ASMs would help rule out non-epileptic events as well as pseudo-drug-resistant (Fig. 1). Epilepsy surgery is a critical option for patients who are candidates, as it can offer sustained seizure freedom and improve quality of life. Early intervention is associated with better cognitive outcomes. Then, it is crucial to evaluate by an expert center if resective epilepsy surgery could be performed, i.e. epilepsy with focal-onset seizure due to an epileptogenic lesion that would not result in severe neurological morbidity if surgically resected. For those who are not surgical candidates, dietary treatments such as the ketogenic diet and neurostimulation methods, including vagus nerve stimulation, provide viable alternatives. These options should be considered based on the patient's age, epilepsy syndrome, and individual benefit-risk ratio.

In DRE patients, there is no evidence-based data for a more effective ASM compared to others or for a more effective combination of ASM due to the absence of head-to-head comparisons of ASM. The ASMs are chosen based on the seizure type, the epilepsy syndrome, and the individual characteristics of each patient. Therefore, there are no guidelines for DRE. The real-life data have provided enough evidence only for one synergistic combination of ASM (valproate-lamotrigine). The advent of precision medicine marks a significant advancement in the field, offering the potential for more targeted and effective treatments. Gene sequencing and cloning have enabled the identification of dysfunctional proteins, paving the way for treatments tailored to specific genetic abnormalities. For example, sodium channel blockers have shown promise in preclinical studies for SCN2A-related epilepsy, and mTOR inhibitors like everolimus have demonstrated efficacy in tuberous sclerosis complex. However, translating these preclinical findings into clinical practice remains challenging, and not all targeted treatments have proven effective in clinical trials. A new generation of precision medicine is starting in the rare pediatric-onset epilepsy. Gene therapy, including antisense nucleotides and viral vector-mediated therapies, represents a frontier in the treatment of genetic epilepsies, such as Dravet syndrome. These therapies hold the promise of addressing the underlying genetic causes of epilepsy, potentially improving both seizure control and cognitive outcomes. However, the long-term efficacy and safety of these approaches are still under investigation. Continuous advancements in genetic research and precision medicine are set to greatly improve outcomes for children with DRE. Although challenges remain, these innovations bring new hope for more effective and personalized treatments, leading to better management and possibly curative therapies in the future.

CRediT authorship contribution statement

Stéphane Auvin: Writing – review & editing, Writing – original draft, Validation, Project administration, Conceptualization. **Nicola Specchio:** Writing – review & editing, Writing – original draft, Validation, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: [Stéphane Auvin is Deputy Editor for *Epilepsia*. He has served as a consultant or received honoraria for lectures from Angelini Pharma, Biocodex, Eisai, Encoded, Grintherapeutics, Jazz Pharma, Neuraxpharm, Nutricia, Proveca, Stoke, Supernus, Takeda, UCB Pharma, Xenon. He has been an investigator for clinical trials for Eisai, Marinus, Proveca, Takeda, UCB Pharma. NS has served on scientific advisory boards for GW Pharma, BioMarin, Arvelle, Marinus and Takeda; has received speaker honoraria from Eisai, Biomarin, Livanova, Sanofi; has served as an investigator for Zogenix, Marinus, Biomarin, UCB, Roche].

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