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INVITED ARTICLE

Precision therapies for genetic epilepsies in 2025: Promises and pitfalls

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Abstract

By targeting the underlying etiology, precision therapies offer an exciting paradigm shift to improve the stagnant outcomes of drug-resistant epilepsies, including developmental and epileptic encephalopathies. Unlike conventional antiseizure medications (ASMs) which only treat the symptoms (seizures) but have no effect on the underlying disease, precision therapies have the potential to suppress not only the seizures but also disabling comorbidities, including cognitive and behavioral abnormalities, which share the same causative mechanisms. Monogenic epilepsies are an attractive target for precision therapies because of their well-defined molecular mechanisms which can be tested in vitro and can be counteracted by specific drugs. Unfortunately, however, for the vast majority of proposed precision therapies, the evidence for their clinical efficacy is either non-existent or limited to uncontrolled observational accounts. Everolimus is the sole precision therapy with a seizure-related indication with class I evidence of efficacy, highlighting the practical and ethical challenges in obtaining high-level evidence. Here, we review the evidence landscape for candidate precision therapies, including repurposed and innovative treatments currently in development, discuss lessons learned from their use, and highlight strategies to improve their application and evaluation in the clinical setting.

Plain Language Summary: Precision therapies offer a new approach to treat drug-resistant monogenic epilepsies, that is, epilepsies caused by a defect in a single gene. Unlike traditional antiseizure medications, precision therapies target the cause of the disease and have the potential to improve not only seizure control but also concomitant conditions such as cognitive and behavioral disorders. To date, the evidence derived from the clinical use of most proposed precision therapies is limited. This review explores current evidence and strategies to advance their development.

KEYWORDS

clinical trials, monogenic epilepsies, targeted therapies, treatment

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1 | INTRODUCTION

Since the discovery of the first epilepsy gene, *CHRNA4*, in a large family with autosomal dominant sleep-related hypermotor epilepsy (ADSHE) in 1995,[1] there has been tremendous progress in epilepsy genetics, arguably like in no other epilepsy field. We now have more than 1000 individual genes responsible for a large variety of Mendelian (monogenic) epilepsies, with additional genes implicated in epilepsies with complex (polygenic) genetic architecture.[2,3] Single-gene pathogenic variants of large effect size are highly prevalent in rare or ultra-rare epilepsies such as the developmental and epileptic encephalopathies (DEEs) and the progressive myoclonus epilepsies (PMEs), as well as in some common focal epilepsies.[4–7]

Identifying a pathogenic variant is a key step in elucidating the functional defect responsible for the disease. This paves the way for the development and implementation of precision therapies, defined herewith as treatments that target specifically the molecular etiology of the disorder or its consequences. Precision therapies have the potential to turn the tide on the stagnant outcomes for many individuals with drug-resistant epilepsy.[8,9] In addition, particularly when applied early in the course of the disease, precision therapies have the potential not only to control seizures but also to ameliorate disabling co-morbidities, which share the same causative mechanisms. This promise is especially alluring for individuals at the severe end of the epilepsy spectrum, such as those with DEEs and PMEs. In these cases, the impact of comorbidities, ranging from developmental delay to cognitive decline, psychiatric disorders, and movement abnormalities, can surpass that of drug-resistant seizures. In other medical fields, advances in genetics have already reshaped treatment approaches. Oncology leads the precision therapy landscape, with treatment emphasis shifting from a tumor's origin to its molecular characteristics.[10,11]

The rational approach to the development of precision therapies consists in: (i) unraveling the biological mechanisms responsible for the clinical manifestations of the disease; (ii) identifying and/or developing treatments that correct the molecular defect or its consequences; (iii) assessing the efficacy and safety of those treatments in relevant preclinical models, as appropriate; and (iv) conducting well-designed clinical trials to show efficacy and safety in affected individuals. The diverse strategies applied to develop these therapies reflect the range of causative genes and mechanisms and include replacing deficient proteins/cofactors and modifying ion channel, receptor, or cell signaling activity.[12] Monogenic epilepsies are a particularly attractive target for precision therapies.[13,14] Well-developed in vitro and in vivo models, including *Drosophila* and zebrafish systems suitable for high-throughput screening, can be used to screen compounds for potential effectiveness.[15,16] Etiologically relevant animal models are also available for further characterization of promising candidate treatments. Advanced treatments directly targeting gene expression, including gene and nucleic acid-based therapies such as antisense oligonucleotides (ASOs), are already in clinical development.[17–19] Repurposing of medications originally approved for other indications also offers a potentially attractive therapeutic option for some of these epilepsies.[20]

Key points

- We provide a critical review of precision therapies for monogenic epilepsies, including therapies in clinical development.
- Proposed precision therapies include repurposed drugs, novel compounds that refine modes of action of existing antiseizure medications, and several nucleic acid-based therapies.
- By targeting the underlying etiology, some of these therapies have the potential to improve not only seizure control but also comorbid conditions which share the same causative mechanisms.
- Evidence on the efficacy of most precision therapies evaluated to date is suboptimal, being based on uncontrolled observational studies or anecdotal reports. The methodology applied to the clinical evaluation of these treatments needs to be improved.

In this narrative review, we discuss efforts and challenges in translating candidate therapies for monogenic epilepsies from "bench to bedside." It would be fair to say that progress has not been as fast as was envisioned 10 years ago.[21] Because comprehensive reviews of precision treatments for these epilepsies are already available,[22,23] we will focus on relevant examples and discuss critically what we have learnt from studies with these treatments, including issues related to study design and interpretative pitfalls in applying available information to the management of individual patients.

2 | THE CURRENT EVIDENCE LANDSCAPE OF PRECISION THERAPIES FOR THE EPILEPSIES

Although there is a vast arsenal of proposed potential precision therapies, most have been studied only in vitro or in animal models, and evidence for their clinical efficacy

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is either non-existent or limited to uncontrolled observations. There are, however, a few treatments that have undergone rigorous evaluation through a variety of study designs.

2.1 | Everolimus, the sole approved epilepsy precision therapy with Class I evidence of efficacy

To date, Class I evidence of efficacy for a precision therapy in epilepsy, that is, evidence from a well-designed double-blind randomized controlled trial (RCT), has only been provided for the mTOR inhibitor everolimus, which is approved in the United States, Europe, and other countries for the treatment of focal seizures associated with tuberous sclerosis complex (TSC).[24] The initial use of mTOR inhibitors targeted non-seizure manifestations of TSC, such as subependymal giant cell astrocytomas and angiolipomas.[25,26] The decision to conduct a RCT to assess its antiseizure activity in TSC patients stemmed from a decade of reports of off-label use of mTOR inhibitors in this indication. EXIST-3 was a double-blind, placebo-controlled, adjunctive-therapy phase III trial in 366 patients aged 2–65 years with TSC-associated focal seizures. The results provided clear evidence of efficacy.[24] Specifically, 40% of patients randomized to the "high exposure group" (target trough blood everolimus concentrations of 9–15 ng/mL) and 28.2% of those in the "low exposure" group (target concentrations of 3–7 ng/mL) achieved at least 50% reduction in seizure frequency, in comparison with 15.1% in the placebo group ($p < 0.0001$and $p < 0.01$, respectively). Although the results were positive, the improvement in seizure control associated with this precision treatment was not greater than that reported in similarly designed trials of some conventional ASMs in patients with focal epilepsies due to other etiologies.[27]

An interesting observation in the EXIST-3 trial was that in both the low- and high-exposure groups, seizure frequency did not plateau at the end of the titration phase; rather, it continued to improve throughout the entire duration of the maintenance period (Figure 1). A dissociation between the time course of blood everolimus levels and clinical response is consistent with the hypothesis of everolimus' antiseizure activity being mediated by an indirect effect (mTOR pathway inhibition), rather than a direct action on neuronal excitability. The continuous improvement in seizure frequency during the maintenance period also suggested that everolimus might have antiepileptogenic or disease-modifying effects, consistent with findings from animal models.[28] However, the hypothesis that everolimus might actually impact favorably on the course of the disease did not find confirmation in a subsequent long-term study where patients were followed for up to 14 years post-randomization.[29] In that study, clinical benefit was apparently retained in most patients for as long as treatment was continued, but there was no evidence for treatment leading to higher seizure freedom rates over time. The proportion of patients who were seizure-free during the last 12 month of follow-up was 9.7%, a finding that might be explained by a sustained symptomatic effect of everolimus, but also by the effect of changes in concomitant antiseizure treatments, or simply the natural course of the disease. Thus, while everolimus fulfilled the promise of being efficacious for TSC-associated focal seizures, its "precise" mechanism of action did not lead to a clearly superior clinical benefit compared with other ASMs. Adverse effects and drug interactions also complicate its clinical use.[30] In a worldwide survey of pediatric neurologists conducted by the International League Against Epilepsy in August 2020, only 1.8% of the 400 respondents considered everolimus as the treatment of choice for a 2-year-old child with TSC-associated focal seizures, and only 3.2% considered it as second-line treatment.[31] Likewise,

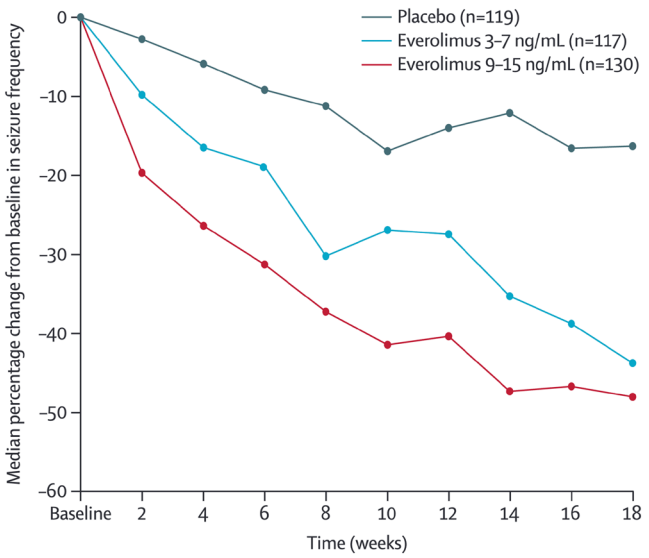


FIGURE 1 Median percentage change from baseline in seizure frequency in EXIST-3, a phase III, randomized, double-blind, placebo-controlled, adjunctive-therapy trial of everolimus in patients with focal seizures associated with tuberous sclerosis complex (TSC). Patients were randomized to placebo or two different target ranges of blood everolimus concentrations. The trial included a 6-week titration followed by a 12-week maintenance period, with dose adjustments guided by blood everolimus concentrations. The improvement in seizure frequency was statistically significant in both everolimus exposure groups compared with placebo (see text). Of note, seizure frequency declined progressively in both everolimus groups throughout the entire duration of the maintenance period. Reproduced from French et al. (2016)[24] with permissions from Elsevier; License Number 596280000185.

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in a recent treatment algorithm for focal seizures in infants and children with TSC, everolimus was only listed as a third-line treatment.[32]

2.2 | High-quality evidence of efficacy may not necessarily require the conduction of an RCT: cerliponase alfa as an example

Whilst placebo-controlled adjunctive-therapy RCTs remain the gold standard in assessing new treatments for epilepsy, there is evolving regulatory flexibility for (ultra-)rare diseases where inclusion of a placebo group may not be feasible or ethical. One example is the development of cerliponase alfa, a precision enzyme replacement treatment for children with neuronal ceroid lipofuscinosis type 2 (CLN2). CLN2 disease is a late-infantile onset inherited neurodegenerative lysosomal storage disease that often presents with treatment-resistant seizures. In the face of a rapidly progressive and fatal disease, exposure to placebo carried an unacceptable risk of delaying potentially life-saving treatment. Moreover, because cerliponase alfa requires delivery by the intracerebroventricular (i.c.v.) route at 2-week intervals, including a placebo group would have exposed children to the risk of infusion device-related complications, such as infection and pleocytosis.

In 2017, the US Food and Drug Administration (FDA) approved cerliponase alfa based on the results of a single-arm, 48-week, open-label, dose escalation study in 24 children aged 3–9 years, whose clinical outcome was compared with that of a separate group of historical controls.[33] The primary endpoint (change in the composite motor-language score of the CLN2 Rating Scale) showed a markedly slower rate of functional decline in the treatment group in comparison to the historical control group ($p < 0.001$). After reviewing the study data, the FDA was unable to establish comparability for the CLN2 language domain scores between the clinical study patients and the historical controls, and therefore the approved indication was limited to "slow the loss of ambulation."[34] However, the treated patients also had a slower decline in scores for the language domain and the four-domain (motor, language, vision and seizures) score, though change in seizure frequency was not independently reported.[33] Initially, cerliponase alfa was only approved for the treatment of symptomatic children 3 years of age and older. Based on newly acquired data, in 2024, the lower age limit was reduced to birth, that is, before the onset of symptoms.[35] Of note, not all manifestations of CLN2 disease seem to be equally influenced by treatment. In particular, retinal degeneration remains progressives, despite treatment with i.c.v. cerliponase alfa.[36]

Although strictly speaking, cerliponase alfa cannot be considered an epilepsy treatment, the lessons learned from its development could well apply to some forms of epilepsy. These include the demonstration that: (i) it is possible to develop treatments that do not have solely a symptomatic effect but also impact favorably on the progression of the disease; (ii) optimal response can be dependent on the treatment being started as early as possible, even at pre-symptomatic stages; (iii) different functional domains may be improved with a single treatment, but the response may not extend to all comorbid conditions; (iv) data from historical controls can be accepted by regulators, but the methodology used for data collection is crucial and needs to be closely replicated when testing a new treatment. In the future, historical controls are likely to be increasingly considered when evaluating novel precision therapies, particularly those targeting progressive disorders. The contribution of the ongoing monogenic epilepsy registries, prospectively documenting the natural history of specific disorders, can be highly valuable in this context.[37]

2.3 | High-quality evidence in individual patients: N-of-1 RCTs

Conducting traditional RCTs in patients with (ultra-)rare epilepsies can be challenging because of the feasibility barriers involved in enrolling a sufficient number of participants to generate adequate statistical power. One way to circumvent this problem is to conduct a N-of-1 RCT, or a series of N-of-1 RCTs.[38] N-of-1 RCTs adjoin the research and clinical goals with the primary aim of improving medical care for an individual with a specific disorder.[39] Distinct from the uncontrolled testing of investigational therapies in an individual patient (sometimes broadly referred to as "N-of-1 trials",[40] though this term should be reserved to within-patient RCTs[41]), N-of-1 RCTs use a multiple crossover within-participant design to optimize the assessment of an intervention by incorporating a control treatment (e.g., placebo), randomization, pre-defined outcomes, rigorous safety monitoring, and statistical analysis. In these trials, each participant is their own control. The N-of-1 RCT methodology leverages repetition of crossovers as a surrogate of sample size to increase statistical power. This approach enables personalized treatments, dosing regimens, and outcomes, and minimizes inter-person heterogeneity bias but comes at the cost of uncertain generalizability to other individuals.

A double-blind, placebo-controlled, N-of-1 RCT of a precision therapy in epilepsy has been reported in a 33-year-old woman with drug-resistant ADSHE due to a pathogenic variant in *CHRNA4*, encoding the nicotinic

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acetylcholine receptor α4 subunit. This single-participant trial demonstrated marked improvement in seizure control with use of a nicotine patch.[42] Subsequent to this trial, uncontrolled case reports and series also reported seizure reduction with transdermal nicotine in a small number of patients.[43–45] As stated in a recent review, however, "further placebo-controlled studies on larger cohorts are needed before considering transdermal nicotine patches in drug-resistant sleep-related hypermotor epilepsy."[46] The authors' personal clinical experience and knowledge of unsuccessful unpublished clinician-led trials of this precision therapy highlights that although a single-participant RCT, through methodological rigor, was able to demonstrate efficacy in that individual, the results could not be extrapolated to the broader population. This limitation has been overcome in other fields, where most N-of-1 trials are published in series, and multiple trials of the same intervention in participants with similar characteristics are aggregated to provide population-level evidence.[47,48]

For a number of proposed precision therapies, initial testing was not motivated by a mechanistic approach, and serendipity played a key role. The nicotine trial in the above-described patient with ADSHE, for example, might not have been conducted had the patient not reported an increase in seizures on cessation of smoking.[42] In fact, the value of a nicotine acetylcholine receptor agonist in a disorder caused by a gain-of-function variant is counterintuitive, and the mechanism of action of nicotine in ADSHE is not fully understood. One hypothesis is that nicotine may desensitize the hyperactive receptor, but mechanisms unrelated to correction of the gain-of-function are possible, as also suggested by a recent report of transdermal nicotine being efficacious in a patient with sleep-related hypermotor epilepsy with no identified pathogenic variant.[49] Overall, these results indicate that in fact, some precision therapies may be less precise than originally thought.

2.4 | Establishing treatment effectiveness through abundant observations

For several metabolic epilepsies due to single-gene pathogenic variants, precision treatments have been established through large amounts of anecdotal and observational accounts. In the glucose transporter 1 deficiency syndrome (GLUT1-DS) caused by pathogenic variants in *SLC2A1*, encoding the glucose transporter protein type 1 in the brain, the ketogenic diet offers an alternative fuel source (ketones) to counteract the impaired glucose transport.[50] Similarly, pyridoxine-dependent epilepsy (PDE-ALDH7A1), caused by pathogenic variants in *ALDH7A1*, is named after its precision therapy (pyridoxine) that bypasses the sequestration of pyridoxal 5′-phosphate, caused by the toxic accumulation of a lysine intermediate metabolite. The volume and quality of observational evidence have resulted in a high level of consensus among experts for the ketogenic diet and pyridoxine to be first-line standard-of-care treatments for GLUT1-DS and PDE-ALDH7A1, respectively.[50,51] Early descriptions of their use reported a close temporal association between treatment initiation and seizure response, as well as the recurrence of seizures with treatment withdrawal, in addition to large effect sizes and high responder rates.[52,53] The comparative affordability and regulatory permissiveness of these dietary treatments contributed to the rapid accumulation of clinician experience and published accounts. Nevertheless, there are subsets of patients who do not respond to these precision therapies, and the mechanisms underlying treatment failure in these patients have not been clearly defined.[54,55]

2.5 | Not all that is precise is effective

Even for promising precision therapies that demonstrate impressive rescue of disease phenotypes in laboratory models, a number of factors can impact clinical response when the same treatments are tested in individuals with epilepsy. Some relate to the characteristics of the treatment, such as pharmacokinetic properties (including pharmacokinetic variability), interactions with concomitantly used medications, and the appearance of dose-limiting intolerance due to off-target effects. Patient-related factors that may influence clinical response include age-related changes in the progression/manifestations of the disease, the deleterious consequences of prior exposure to uncontrolled seizures for a prolonged period, and polygenic influences on the expression of disease and on treatment responsiveness.[13,56] Other potential confounders arise from suboptimal use of the treatment (for example, suboptimal dosing regimens or titration rates), inadequate study designs (including failure to use appropriate controls) or lack of validated assessment tools, particularly for comorbid conditions. Some of these issues are briefly discussed in Section 4.

2.6 | Variability in clinical response and the role of phenotype: quinidine in KCNT1-related epilepsies as an example

Although rarely executed, well-designed high-quality clinical trials may ultimately show that a putative precision therapy may not only be ineffective, but also

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associated with significant harm. This was highlighted by a placebo-controlled RCT of the potassium channel blocker quinidine in patients with a severe form of ADSHE due to gain-of-function mutations in the potassium channel gene *KCNT1*.[57] The trial was motivated by the demonstration that quinidine can reverse the functional defect in *Xenopus* oocytes expressing the mutated channels,[58] and by case reports of dramatic seizure reduction in children with epilepsy of infancy with migrating focal seizures (EIMFS), a severe DEE also caused by gain-of-function pathogenic variants in *KCNT1*.[59,60] When assessing the value of quinidine in six ADSHE patients aged 15–54 years, Mullen et al.[57] found that dosing was constrained by prolonged QT intervals, despite very low or barely detectable serum quinidine levels. In the face of the dosing limitations, quinidine had no clinical effect on six patients assessed, despite the patients' pathogenic variants demonstrating in vitro response.[57,58] Although the small sample size, with five of six patients being from one family, limits extrapolation of these results to other populations (e.g., younger patients, patients with EIMFS), the study highlighted the potential cardiac toxicity of quinidine, and suggested that patients carrying certain *KCNT1* variants may be hypersensitive to the cardiac effects of the drug. A systematic review of 27 studies including a total of 82 quinidine-treated patients with 33 different pathogenic variants in *KCNT1* reported a ≥50% improvement in seizure frequency in one-quarter of patients, based on uncontrolled observations.[61] The apparent response to quinidine varied across individuals, even among those sharing the same mutation, and did not correlate with age or epilepsy syndrome,[61] although patients with ADSHE (mostly participants in the trial by Mullen et al.[57]) were generally unresponsive. Of note, the presence of pathogenic variants sensitive to quinidine in vitro did not necessarily predict clinical effectiveness, but lack of responsiveness in vitro did appear to predict lack of efficacy in vivo. As for other precision treatments, possible reasons for the limited correlation between in vitro and in vivo data might be explained by confounders such as differences in dose, individual sensitivity to adverse effects, drug–drug interactions, influence from other gene expression, and use of suboptimal in vitro and in vivo assessment protocols.

3 | CANDIDATE PRECISION THERAPIES TESTED IN THE CLINICAL SETTING

Several repurposed and novel precision treatments have undergone at least some limited clinical testing, with a few being assessed in formal clinical trials. The list of compounds discussed in this section is not exhaustive, but aims to reflect the breadth of approaches being considered, including some innovative therapies currently under development (Table 1).

3.1 | Repurposed drugs – the "low-hanging fruit"?

A number of drugs approved for other indications have been proposed for repurposing as precision therapies for monogenic epilepsies. Repurposing is potentially more time- and cost-efficient than novel drug discovery, with expedited progress through pre-clinical testing, clinical safety and pharmacokinetic studies (especially required when dealing with medications only approved for adults, and envisaged for epilepsy use in pediatric populations), and dose-finding efficacy studies. In fact, most repurposed treatments have not entered formal clinical development, and they have only been tested in a very small number of patients (Table 2). For some, such as isradipine for *CACNA1D*-related DEE, no evidence of efficacy has been provided in preliminary clinical testing despite a theoretical rationale and encouraging data from in vitro experiments.[62] For others, signals of clinical efficacy have emerged, but the data are generally difficult to interpret because of methodological shortcomings, particularly reliance on retrospective uncontrolled observations and substantial risk for bias.

One reason for the limited quality and quantity of the evidence is that access to existing medications for off-label use is often constrained by cost and regulatory barriers, affecting both patented and generic drugs. However, while the financial incentives to investigate new indications for existing compounds are often modest, largely due to challenges in securing patent exclusivity, there can be significant incentives for orphan drug development. These extend to creating novel derivatives of established medications, such as glycerol phenylbutyrate ("Ravicti"), a derivative of the originally marketed product, sodium phenylbutyrate.[95] Glycerol phenylbutyrate is currently approved for the chronic treatment of patients with urea cycle disorders who cannot be managed by dietary protein restriction and/or supplementation alone. Phenylbutyric acid (4-PB, the active principle present in the circulation after administration of either sodium phenylbutyrate and glycerol phenylbutyrate) has been proposed as a precision therapy for patients with *SLC6A1*-DEEs caused by loss-of-function mutations in the *SLC6A1* gene, encoding the γ-aminobutyric acid (GABA) transporter 1 (GAT-1). In *SLC6A1* variant-bearing patient cells, 4-PB, which acts

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TABLE 1 Novel experimental precision therapies under clinical development with publicly available information.

Investigational therapy (company)	Mechanism	Indication	Status (ClinicalTrials.Gov ID)
Small molecules			
Relutrigine/PRAX-562 (Praxis)	Selective inhibitor of the persistent sodium currents	*SCN2A-/SCN8A*-DEEs (GoF)	Phase II (NCT05818553)
Radiprodil (GRIN Therapeutics)	Negative allosteric modulator of NR2B subunit-containing NMDA glutamate receptors	*GRIN*-related disorders (GoF)	Phase Ib (NCT05818943)
Biologic therapies			
Clervonafusp alfa/VAL-1221 (Parasail)	Fusion protein comprising the Fab portion of a recombinant humanized cell-penetrating antibody (3E10 IgG) and recombinant human acid alpha glucosidase (rhGAA), leading to degradation of Lafora bodies	Lafora disease (*EMP2A/EMP2B* LoF)	Phase II (NCT05930223)
Nucleic acid-based therapies			
Zorevunersen/STK-001 (Stoke)	ASO upregulating $Na_v1.1$ protein expression	Dravet syndrome (*SCN1A* LoF)	Phase I/II (NCT04442295, NCT04740476)
Elsunersen/PRAX-222 (Praxis)	ASO down-regulating Nav1.2 expression	*SCN2A*-DEEs (GoF)	Phase I/II (NCT05737784)
ION-582 (Ionis)	ASO upregulating *UBE3A* expression	Angelman syndrome (maternally inherited *UBE3A* allele LoF)	Phase I/IIa (NCT05127226)
GTX-102 (Ultragenyx)	ASO inhibiting the expression of the *UBE3A* antisense transcript to upregulate paternal *UBE3A* expression	Angelman syndrome (maternally inherited *UBE3A* allele LoF)	Phase III (NCT04259281, NCT06415344, NCT06617429)
ION-283 (Ionis/Noventia)	ASO downregulating *GYS1* expression, reducing glycogen synthesis, and thereby Lafora body accumulation	Lafora disease (*EMP2A/EMP2B* LoF)	Phase I/II (NCT06609889)
ETX-101 (Encoded)	AAV-delivered gene therapy comprising a GABAergic regulatory element (reGABA) and an engineered transcription factor that increases transcription of the *SCN1A* gene	Dravet syndrome (*SCN1A* LoF)	Phase I/II (NCT05419492, NCT06112275, NCT06283212)

Abbreviations: AAV, Adeno-associated virus; ASO, antisense oligonucleotide; DEE, developmental and epileptic encephalopathy; GABA, gamma-aminobutyric acid; GoF, gain-of-function; LoF, loss-of-function; NMDA, N-methyl-D-aspartate.

as a chaperone, was shown to reduce endoplasmic reticulum retention of the mutant protein, increase wild-type protein trafficking and restore GABA uptake.[96] Glycerol phenylbutyrate, a slow-release 4-PB formulation, has been tested in an open-label trial of 20 individuals with either *SLC6A1*- or *STXBP1*-DEEs (NCT04937062). The preliminary results, published in preprint, reported on safety and tolerability (primary endpoint) as well as seizure outcomes. There were six serious adverse events, of which one (metabolic acidosis) attributed to 4-PB led to treatment discontinuation. Of the 19 remaining patients, 18 opted for extended use for at least 2 years. A reduction in events (classified as seizures or "spells") were described in six of 10 participants with *SLC6A1*-DEEs after 10 weeks of treatment.[97] Although findings have raised significant enthusiasm among consumers, the uncontrolled open-label design and assessment of seizure frequency by caregiver interview are susceptible to various confounders, such as placebo effects and the natural variation in seizure frequency. The story of glycerol phenylbutyrate provides a good example of challenges involved in the use of some potential precision treatments. In absence of robust evidence of efficacy, the use of the compound for the off-label treatment

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TABLE 2 Some potential precision therapies with repurposed medications for which results of clinical testing in patients with monogenic epilepsy have been reported.

Gene (protein, alteration of function)	Repurposed medication	Putative mechanism of action	Evidence/comments and references
ATP1A2 (Na^+/K^+ ATPase pump, disruption of Na^+/K^+ homeostasis putatively leads to decreased EAAT activity and reduced glutamate uptake from the synaptic cleft)	Memantine	Inhibition of glutamatergic excitotoxicity through blockade of NMDARs	In a retrospective report of three girls with *ATP1A2*-related DEE, memantine was associated with reduced seizure frequency in one patient and improvement in comorbid symptoms (ataxia and/or attention/alertness) in the others.[63] Improvement of comorbid symptoms has also been described in other reports[64]
CACNA1D ($Ca_v1.3$, a L-type voltage-gated calcium channel; gain-of-function)	Isradipine	Blockade of neuronal L-type calcium channels	In a 38-month-old boy with *CACNA1D*-related DEE, isradipine failed to improve seizure frequency or tremors, despite sensitivity of the mutated channel to isradipine in vitro[62]
CHRNA2/CHRNA4/CHRNB2 (cholinergic receptor nicotinic subunits; gain-of-function)	Nicotine	Desensitization of mutated neuronal nicotinic acetylcholine receptors	A placebo-controlled N-of-1 RCT demonstrated efficacy in one patient with *CHRNA4*-ADSHE.[42] Retrospective studies also reported seizure reduction in 7 ADSHE patients who harbored *CHRNA2*, *CHRNA4* and *CHRNB2* pathogenic variants[43,45,65]
	Fenofibrate	Activation of peroxisome proliferator-activated receptor alpha (PPARα), which negatively modulates β2-subunit containing nicotinic acetylcholine receptors	A prospective uncontrolled trial showed marked improvement in seizure frequency in 5/5 patients with ADSHE. Fenofibrate was also associated with improved seizure control in 7/7 patients with SHE[66]
GABRA1/GABRB3/GABRG2 (GABA-A receptor subunits; loss-of-function)	Vinpocetine	Correction of loss-of-function in GABA-A receptors	In retrospective single-patient reports, vinpocetine was associated with reduced spike–wave discharges and improved language and behavior in a woman with *GABRB3*-related LGS[67]; seizure freedom and improved psychiatric comorbidities in a young man with *GABRA1*-focal epilepsy[68]; periods of temporary (1 month) seizure cessation in a boy with *GABRG2*-epilepsy with frequent GTCS and absence seizures[69]
GRIN1/GRIN2A/GRIN2B/GRIN2D (NMDAR subunits; loss-of-function)	L-Serine	NMDAR stimulation	In an open-label phase 2A study of L-serine in *GRIN*-related disorders, 5/18 children who had no clinical seizures at baseline showed disappearance of epileptiform EEG activity, but another child had their first seizure on treatment with L-serine.[70] One of two children with active epilepsy had reduced seizure frequency on L-serine.[70] In a retrospective case-series of children with *GRIN*-related encephalopathy, 1/6 with epilepsy had seizure reduction, and two others (one with SWAS and another with generalized epileptiform discharges) had EEG improvements only.[40] In a young boy with *GRIN2A* DEE-SWAS, seizure frequency decreased markedly within 1–2 days of L-serine treatment[71]

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TABLE 2 (Continued)

Gene (protein, alteration of function)	Repurposed medication	Putative mechanism of action	Evidence/comments and references
GRIN1/GRIN2A/GRIN2B/GRIN2D (NMDAR subunits; gain-of-function)	Memantine	NMDAR blockade	There have been 11 retrospective studies reporting memantine use in 15 cases of *GRIN*-related epilepsy. Marked (>75%) seizure reduction was reported in four children aged 20 months to 3 years with *GRIN2A*-IESS,[72] *GRIN1*-EOEE,[73] *GRIN2D*-EOEE,[74] and *GRIN2B*-IESS.[75] Four further patients had modest (<75%) seizure reduction.[76–79] Some of the responders also showed improvements in neuropsychological comorbidities.[73,76,79] Memantine was ineffective in seven patients with a variety of *GRIN*-related DEEs[76,77,80,81]
KCNA1/KCNA2 (Kv1.1 and Kv1.2 voltage-gated potassium channel subunits; gain-of-function)	4-Aminopyridine	Blockade of neuronal K_v1.1 and Kv1.2 potassium channels	In a retrospective case-series, 4-aminopyridine was associated with seizure reduction in 6/8 patients with active *KCNA2*-related generalized epilepsy. Ataxia and cognitive comorbidities were also improved.[82] 4-Aminopyridine was also associated with an increase in seizure-free days in an infant with drug-resistant *KCNA1*-focal epilepsy[83]
KCNC1 (Kv3.1 voltage-gated potassium channel subunit; gain-of-function)	Fluoxetine	Blockade of neuronal K_v3.1 potassium channels	In an 8-year-old girl with *KCNC1*-DEE, use of fluoxetine was associated with cessation of seizures and improvement in balance, gross motor skills, and oculomotor coordination[84]
KCNT1 (Slack sodium-gated potassium channel subunits; gain-of-function)	Quinidine	Slack potassium channel blockade	In 27 studies including a total of 82 patients with *KCNT1*-related epilepsies (mostly EIFMS, DEEs, and ADSHE), about a quarter showed an apparent improvement in seizure control on quinidine (see text).[61] Quinidine seems to be ineffective in ADSHE[85] due to dose-limiting cardiotoxicity, mainly based on data from a small placebo-controlled trial[57]
	Fluoxetine	Slack potassium channel blockade	In an 18-year-old woman with *KCNT1*-related drug-resistant focal seizures, introduction of fluoxetine was associated with seizure cessation and improved behavior and mood[86]
KCNT2 (Slick sodium-gated potassium channel subunit; gain-of-function)	Quinidine	Slick potassium channel blockade	Quinidine use in a 9-year-old girl with *KCNT2*-related LGS was associated with transient reduction in seizure frequency and persisting improvement in EEG and alertness[87]
NF1 (neurofibromin, a protein that negatively regulates MAPK pathway activity; gene defect leads to MAKP activation)	MEK inhibitors (selumetinib and trametinib)	MAPK/ERK inhibition	MEK inhibitors led to seizure cessation in two children with epilepsy and progressive optic pathway glioma on the background of neurofibromatosis type 1. The drugs used were selumetinib in an 8-year-old boy with focal epilepsy[88] and trametinib in 9-year-old girl with tonic seizures and GTCS.[89] In the girl, seizures recurred when trametinib was withdrawn due to toxicity
PCDH19 (protocadherin-19, a calcium-dependent adhesion glycoprotein; loss-of-function)	Ganaxolone	Reduced neurosteroidogenesis including low allopregnanolone levels, has been implicated in *PCDH19*-clustering epilepsy. Like allopregnanolone, ganaxolone acts as a positive allosteric modulator of GABA-A receptors	In a placebo-controlled RCT in 21 girls with *PCDH19*-clustering epilepsy, median percentage change in seizure frequency was −61.5% with ganaxolone and −24.0% with placebo.[90] The difference did not reach statistical significance, possibly due to large variability in seizure clustering intervals

(Continues)

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TABLE 2 (Continued)

Gene (protein, alteration of function)	Repurposed medication	Putative mechanism of action	Evidence/comments and references
SCARB2 (lysosomal integral membrane protein-2; impaired β-glucocerebrosidase trafficking leads to toxic accumulation of GL1 and its deacylated derivative glucosylsphingosine)	Miglustat	Inhibition of glucosylceramide synthase, an essential enzyme for the synthesis of most glycosphingolipids	Retrospective reports described the outcome of miglustat use in five adults with *SCARB2*-associated action myoclonus–renal failure syndrome. Of those, two had a reduction of myoclonic jerks and seizures,[91,92] two had worsening of ataxia/tremor,[93] and one did not tolerate miglustat due to vomiting and diarrhea[94]

Note: The list should not be regarded as exhaustive. For additional information, please refer to recent reviews.[26–28]

Abbreviations: ADSHE, autosomal dominant sleep-related hypermotor epilepsy; DEE, developmental and epileptic encephalopathy; EAAT, excitatory amino acid transporters; EIFMS, epilepsy of infancy with migrating focal seizures; EOEE, early-onset epileptic encephalopathy; ERK, extracellular signal-regulated kinase; GABA-A, γ-aminobutyric acid subtype A receptors; GL1, β-glucocerebroside; GTCS, generalized tonic–clonic seizures; IESS, infantile epileptic spasms syndrome; LGS, Lennox–Gastaut syndrome; MAPK, mitogen-activated protein-kinase; MEK, abbreviation for MAPK/ERK kinase; NMDAR, N-methyl-D-aspartate receptor; RCT, randomized-controlled trial; SHE, sleep-related hypermotor epilepsy; SWAS, spike–wave activation in sleep.

of *SLC6A1*-DEEs must be carefully weighed against its high cost (listed in the United States for >$700 000 per year for a single patient[98]) and known risks, including severe metabolic acidosis.

3.2 | Novel precision treatments acting on established ASM targets

3.2.1 | Sodium channel blockers with selectivity for the persistent sodium current

PRAX-562 is a blocker of voltage-gated sodium channels, an established target of many existing ASMs. Compared with traditional ASMs, PRAX-562 shows enhanced use-dependent blockade and increased selectivity for the persistent sodium current,[99] a pathological contributor to neuronal hyperexcitability implicated in several gain-of-function sodium channelopathies.[100–102] PRAX-562 is in phase 2/3 development for the treatment of *SCN2A*- and *SCN8A*-DEEs (NCT05818553).[103]

3.2.2 | Second-generation Kv7.2/7.3 potassium channel activators

Efforts are also underway to develop second-generation K_v7.2/7.3 potassium channel activators with improved efficacy and safety. The first-in-class K_v7.2/7.3 blocker retigabine (also known as ezogabine) was marketed for the broader indication of adjunctive treatment of focal seizures in adults with epilepsy. It showed promise as a precision therapy for neonatal onset *KCNQ2*-DEEs, counteracting the loss-of-function of K_v7.2 channels in *KCNQ2* pathogenic variants. Two case series and a case report totaling 20 patients suggested that retigabine reduced seizures associated with *KCNQ2*-DEE, especially if given before 6 months of age.[104–106] Although retigabine was withdrawn from the market for commercial reasons after it was found to cause off-target ophthalmological/dermatological toxicity, it validated K_v7.2/7.3 channels as therapeutic targets. A randomized double-blind adjunctive-therapy placebo-controlled trial of a pediatric-specific formulation of retigabine (XEN496) in patients with *KCNQ2*-DEE was prematurely terminated by the sponsor in 2023, for reasons unrelated to safety (NCT04639310).[107] Other K_v7.2/7.3 channel openers, including azetukalner (XEN1101), BHV-7000, pynegabine, and CB-003 are undergoing clinical development for drug-resistant epilepsies.[107] Although the development of these compounds is currently targeting common epilepsies, there would be a clear rationale for also testing their potential value as precision therapies for patients with *KCNQ2*-DEE.

3.2.3 | Nonselective N-methyl-D-aspartate (NMDA) receptor modulator

Although NMDA receptor antagonists such as ketamine and memantine have demonstrated potential in the treatment of seizures, their use has been limited by a range of behavioral and cardiovascular off-target effects.[108] Radiprodil is a selective negative allosteric modulator of the NR2B subunit-containing NMDA receptors, with the potential to improve clinical outcomes in patients with *GRIN*-related disorders caused by gain-of-function mutations in genes encoding NMDA receptor subunits (*GRIN1*, *GRIN2A*, *GRIN2B*, *GRIN2D*). Currently, ongoing phase Ib open-label trials are investigating its use in *GRIN*-related disorders, with separate cohorts for patients with and without seizures, as well as in patients experiencing seizures associated with

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focal cortical dysplasia or TSC.[109] Topline results from the Honeycomb open-label trial of radiprodil in 15 patients with GRIN-related neurodevelopmental disorders reported a median 86% reduction in seizure frequency from baseline.[110]

3.3 | Nucleic acid-based therapies

Nucleic acid-based therapies aim to correct the functional consequences of gene defects through gene inhibition, activation, modulation, replacement, or editing. Most of these therapies currently involve the use of ASOs. ASOs modulate disease pathways by targeting noncoding RNAs, with the potential to be tailored for specific pathogenic variants, epitomizing precision medicine.[17] Such was the case of milasen, an ASO developed to increase normal splicing, created for and named after an individual with fatal neuronal ceroid lipofuscinosis 7 (CLN7) who harbored a heterozygous *MFSD8* pathogenic variant causing mis-splicing.[111] Although seizure frequency decreased by >50% during 1 year of treatment, the patient died from disease progression.

ASOs have become an important component of the therapeutic armamentarium for a number of neurological diseases,[112] and their potential for the treatment of DEEs has been emphasized.[113] In fact, several ASOs targeting specific DEEs have reached clinical development (Table 1), and some of these are briefly discussed below. For compounds for which preliminary data have been reported, the preliminary results are very promising. A disadvantage these therapies have relates to the need for intrathecal administration at regular intervals, and the potential adverse effects related to the route of administration. Although favorable safety profiles have been generally reported to date, cases of non-communicating hydrocephalus have been described in patients administered ASOs for *KCNT1*-related epilepsy,[114] Huntington's disease[115] and spinal muscular atrophy.[116] The mechanism underlying this adverse event is unclear.

3.3.1 | Dravet syndrome

For Dravet syndrome, Stoke Therapeutics is developing zorevunersen (STK-001), an ASO that upregulates the functional *SCN1A* allele and thereby increases the expression of the voltage-gated sodium channel $Na_v1.1$ protein expression.[109] The aim is to counteract the loss-of-function effects of the causative heterozygous *SCN1A* pathogenic variants in these patients. In two open-label phase I/IIa studies,[109] 81 children and adolescents with Dravet syndrome received either a single or multiple ascending doses of zorevunersen intrathecally. Convulsive seizure frequency was reduced in a dose-dependent manner, and preliminary data of extension studies showed improvements in measures of cognition, behavior, and clinical global impressions.[117] In the phase I/IIa studies, 30% of participants experienced a treatment-emergent adverse event. Most were unrelated to the drug, but suspected unexpected serious adverse reactions (SUSARs, not further detailed) were reported in one patient. Elevations of CSF protein levels were more frequent in the extension studies than in the phase I/IIa studies, and led to the discontinuation of treatment in one patient.[109] The protocol of a phase 3 randomized, double-blind, sham-controlled, 60-week trial of zorevunersen in Dravet syndrome has been finalized recently following discussion with United States, European, and Japanese regulators.[118]

Gene-editing technologies are also entering clinical development. Safety and efficacy studies of ETX101, an adeno-associated virus vector-based gene therapy, have been initiated in infants and children with *SCN1A*-positive Dravet syndrome (NCT06112275; NCT06283212, NCT05419492).[19]

3.3.2 | Lafora disease

Lafora disease, a PME, is caused by recessive pathogenic variants in either *EPM2A* (encoding laforin) or *EPM2B* (encoding malin), both leading to an indistinguishable phenotype with the pathological hallmark of intracellular abnormal glycogen deposits (Lafora bodies).[119–122] Advances in elucidating the pathophysiology of this disease have enabled precision therapy efforts to inhibit glycogen synthesis in the central nervous system. A candidate target is the *GYS1* gene, which encodes the muscle isoform of glycogen synthase involved in the synthesis of glycogen in the brain.[123–126] A phase I/II clinical trial of ION283 (NCT06609889), a *GYS1* inhibiting ASO, was initiated following demonstration of its effectiveness in preventing the formation and accumulation of Lafora bodies and slowing disease progression in rodent models.[125,127] A campaign organized by the Chelsea's Foundation, a "team of Lafora disease family and friends dedicated to finding a cure", already collected over $900 000 in charitable donations out of a target of $1.5 million to support the investigator-sponsored first-in-human trial of ION283.[128]

An alternative non-nucleic acid-based treatment for Lafora's disease targeting glycogen synthase (Clervonafusp alfa or VAL-1221) has also entered clinical development. This compound is a polyglucan-degrading enzyme which is administered by intravenous infusion.[129] A phase II

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open-label study investigating this compound is planned (NCT05930223).[130]

3.3.3 | Angelman syndrome

In Angelman syndrome, which is caused by loss-of-function pathogenic variants in the maternal *UEB3A* gene, clinical trials have been initiated with two ASOs designed to increase the expression of the paternal (functional) *UEB3A* gene. ION-582 (NCT05127226) and GTX-102 (NCT04259281) are two ASOs designed to increase the expression of the normal paternal *UEB3A* gene.[131,132] Topline data of phase I/II trials with these ASOs have already been disclosed, with press releases signaling intention to progress to pivotal phase III trials.[131,132]

4 | ADVANCING PRECISION THERAPIES FOR EPILEPSY: CHALLENGES AND POTENTIAL SOLUTIONS

4.1 | Variability in clinical response

Translating discoveries in epilepsy genetics into effective treatments for patients is a challenging journey. The field of epilepsy genetics has evolved beyond single pathogenic variants in coding regions, to encompass a nuanced array of rare and common variants, somatic mosaicism, repeat expansions, and non-coding region variants.[3] New molecular insights have also shown how genetic expression can be influenced by complex neurobiological systems.[12] Even for the "monogenic" epilepsies, the single pathogenic variant of large effect size interacts with the individual's genetic background ("common polygenic risk") and with epigenetic and environment factors to produce a wide variety of clinical manifestations across different individuals.[56,133–135] The same factors can also explain why the effectiveness of precision therapies can vary significantly across individuals sharing the same genetic defect. Variability in response may also occur within individuals due to factors such as brain maturation, age-related pharmacokinetic changes, and drug interactions with concomitant medications.

In vitro experiments and studies in animal models are useful screening tools to identify potential treatments. Although these models provide important insights about the consequences of the pathogenic variant and their potential responsiveness to a specific treatment, they capture only limited aspects of the "therapeutic triad" of individual, disease, and treatment. Differences in therapeutic response can arise not only from patient-related variables, but also from treatment-related factors such as pharmacokinetic variability and off-target effects. Ultimately, the clinical value of precision treatments can only be determined by high-quality studies in patients with the target disease.

In the future, challenges arising from variability in response can be addressed by identification of appropriate clinical and laboratory biomarkers, including additional genetic data, electrophysiological measures, neuroimaging, metabolomic and proteomic data that may serve as predictors of treatment response or disease trajectory.[136–138] Emerging artificial intelligence-driven approaches enable the identification of multimodal biomarker signatures from high-dimensional datasets, facilitating more precise patient selection and therapeutic monitoring.[139] Clinical validation of these biomarkers is required.

4.2 | Suboptimal quality of available evidence

The suboptimal design and reporting of clinical studies in this area contribute significantly to the heterogeneity of published outcome data. The vast majority of epilepsy precision therapy studies conducted to date did not include appropriate control groups, which makes the data difficult to interpret. Improvements can be mistakenly attributed to the treatment when, in fact, they may be due to regression to the mean or a placebo effect.[140] Negative results could be due to suboptimal dose selection or suboptimal evaluation of treatment response (e.g., inadequate duration of follow-up). In retrospective observational studies and case reports, outcome measures during baseline and treatment are variably documented, with a high risk of recall bias. Reporting bias is also a factor because negative outcome data are less likely to be published.

There is clearly a need to improve the methodology applied to the clinical testing of precision treatments in epilepsy. A controlled design should be incorporated whenever possible, and relevant examples of suitable designs have been discussed in the previous sections of this article. It is acknowledged that there are situations in which the use of a putative precision treatment under uncontrolled conditions is justifiable, and the value of these data in providing a signal of potential efficacy should not be underestimated. The most notable example of this scenario relates to the off-label use of repurposed medications in an effort to ameliorate disabling symptoms in individuals with severe drug-resistant epilepsy. Yet, it would be desirable for these therapeutic trials to be recorded prospectively, ideally by establishing collaborative networks and dedicated registries.[141] This would ensure that critical information on patients' characteristics, treatment

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modalities, and clinical response is collected systematically, thereby permitting analysis of aggregated data and the subsequent conduction of follow-up studies using a controlled design whenever appropriate. An approach to the selection of trial design for monogenic epilepsy treatments is suggested in Figure 2.

While emphasis has often been placed on seizure control, non-seizure outcomes which can impact quality of life more than seizures, for example, developmental delay, behavioral disturbances, and movement disorders, need to be evaluated as appropriate. Defining meaningful outcome measurements of neurodevelopment/cognition is challenging, especially in populations with severe impairment.

4.3 | Cost and global access

Even when precision therapies are available, implementation may be limited by affordability.[142] Although repurposed medications may provide a cost-effective alternative to drugs developed specifically as precision treatments for epilepsy, not all repurposed therapies are inexpensive, and reimbursement mechanisms are often subject to administrative hurdles, leading to inconsistencies in market access across different healthcare systems.[143] Advocacy initiatives from patient organizations and healthcare professionals are necessary to improve access to these treatments. With an expected exponential increase in the number of available orphan drugs, even high-income countries will be unable to cover the costs of some treatments (e.g., patient-specific ASOs priced at >$1 million/patient/year.)[144] Still, there is optimism that drug development pipelines, such as those for ASOs, will become more cost-efficient,[145] and that some gene therapies may offer long-lasting effects. Reimbursement decisions will require clinical and economic data, including cost-effectiveness analyses, within a robust ethical framework.

Sadly, issues of cost and affordability are even more challenging in low- and middle-income countries, where

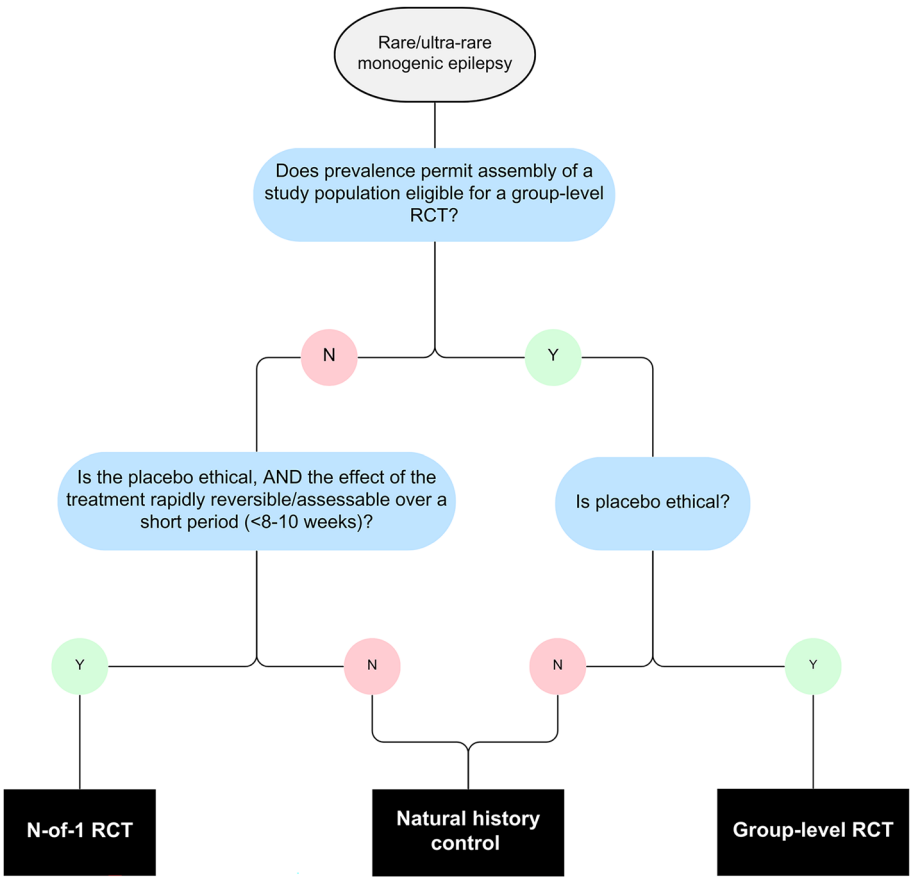


FIGURE 2 Study design considerations for treatment trials in monogenic epilepsies. Although the group-level placebo-controlled RCT remains the gold-standard, this design may not be applicable to many (ultra-)rare monogenic epilepsies due to sample size restrictions. N-of-1 RCTs use multiple crossovers as a surrogate to increase power, and may be especially suitable for treatments with short and reversible effects and clinically static diseases. Where use of placebo is not acceptable/ethical, such as in scenarios involving rapidly progressive neurological disorders, or the need for prolonged (>6 to 12 months) treatment to demonstrate a clinically significant effect, natural history cohorts may act as an alternative control. RCT, randomized controlled trial.

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the majority of people with epilepsy live. Apart from barriers related to the cost of medicines, the foundational step of genetic testing required to identify candidates for precision therapies remains largely inaccessible in these settings, making equitable implementation of these advances particularly challenging on a global scale.

5 | CURRENT ROLE OF PRECISION THERAPIES IN CLINICAL MANAGEMENT

Despite the challenges and limitations outlined above, awareness of the potential value of precision treatments for (ultra-)rare monogenic epilepsies is increasing rapidly. As emphasized in a recent Italian Delphi consensus paper, identifying the underlying etiology (e.g., genetic) is crucial for guiding therapeutic choices and predicting outcomes in the DEEs.[146] Steps for a correct application of precision treatments have also been clearly outlined.[14] Of note, the treatment implications of a molecular genetic diagnosis are not limited to selection of precision treatments, but extend to avoidance of potentially harmful antiseizure medications (ASMs), as in the case of sodium channel blockers in epilepsies caused by loss-of-function *SCN1A* mutations.[147] Additionally, molecular diagnosis may end the "diagnostic odyssey" for patients and families and enable accurate genetic counseling.

Data on the current use of precision therapies in the management of patients with monogenic epilepsies are still relatively scarce.[142,148,149] In a retrospective evaluation of medical records from a tertiary level center in Denmark, 53 of 101 patients with a putative diagnosis of monogenic epilepsy were deemed to be potentially eligible for "precision therapy approaches."[148] These were implemented in 32 patients and 30 of them (93%) experienced a ≥50% seizure reduction, including 4 who became seizure-free. The definition of "precision therapy" in this study, however, was rather broad and included use of ASMs such as fenfluramine and cannabidiol, which hardly meet criteria for an etiology-targeting treatment. More sobering results have emerged from a systematic survey of 293 patients with epilepsy with a molecular genetic diagnosis at 6 specialized centers across the UK, Italy and Germany.[149] A genetic diagnosis prompted treatment changes in 94 individuals (32%), though these did not necessarily involve precision therapies targeting the underlying pathophysiological mechanisms. Precisions therapies were available for 56 patients but were only tried in 33, 10 of whom (30%) experienced a >50% seizure reduction. In another study from a Belgium, precision therapies were considered to be feasible for 20 of 34 patients with monogenic epilepsies, but they were only tried in 11, mostly with some benefit.[142] Main reasons for not trying precision therapies in the remaining patients were lack of reimbursement of the medication for an epilepsy indication, and the treatment being only available in clinical trials.

Overall, a review of the available evidence indicates that the utilization of precision therapies for monogenic epilepsies remains limited. Measures that could improve their effective implementation include the development of unifying definitions of precision therapies, the establishment of publicly accessible databases with information on the functional effect of gene variants, advocacy initiatives to increase availability and reimbursement of these treatments, and broadening access to innovative clinical trials.[142] Design and execution of high-quality clinical trials are among the most important prerequisites, because the evidence base supporting the use of many proposed precision therapies is clearly suboptimal.

6 | CONCLUSIONS AND FUTURE PERSPECTIVES

Precision therapies have the potential to transform the treatment of monogenic epilepsies. Despite the paucity of high-quality evidence to support the use of most of these therapies, research in this area is thriving. Steady strides are being made toward overcoming the translational challenges in bringing precision therapies to clinical application. Past failures and even negative results are yielding critical insights that inform a more rational approach to preclinical and clinical research. Increasingly refined in vitro and in vivo models—such as patient-derived induced pluripotent stem cell (iPSC) systems, organoids, and genetically engineered animal models—are enhancing the predictive validity of preclinical testing.[150] Advances in molecular and systems neuroscience are driving a more nuanced understanding of the biological underpinnings of phenotypic heterogeneity and variable treatment response, enabling more precise stratification of patient subgroups. Parallel progress in biomarker discovery, including molecular, electrophysiological, and imaging-based readouts, coupled with the application of artificial intelligence, is set to revolutionize both patient selection and endpoint assessment in clinical trials. Most notably, the therapeutic landscape is expanding to increasingly include novel and more selective targeted therapies, such as nucleic acid-based therapies.[19,113] Collectively, these advances are accelerating the path toward clinically meaningful, disease-modifying treatments with the potential to transform the standard of care in monogenic epilepsies.

For these efforts to be successful, however, it is essential that the clinical value of precision therapies is established through rigorous methodology. Innovative trial designs

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are starting to be applied to generate robust evidence for therapies in (ultra-)rare diseases.[151–154] Natural history cohorts are emerging as an alternative control, especially for progressive and severe diseases or invasive routes of administration where placebo is not an acceptable option. High-quality data collection, careful statistical planning, and hybrid trial design may minimize the inherent biases from a lack of randomization. At the other end of the spectrum, single-participant "N-of-1" RCTs can address the challenges of conducting high-quality randomized trials in (ultra-)rare populations, allowing personalization of dose, duration of treatment and outcome measures to account for inter-patient phenotypic variability. Other approaches that permit rigorous assessment of treatment response under controlled conditions include adaptive designs,[153,155,156] blind-start designs,[157] and master protocol designs.[158] A master protocol of N-of-1 trials in patients with monogenic epilepsies has been recently set in place by our group at the University of Melbourne, Australia. Use of biomarkers and prediction models supported by artificial intelligence can supplement information derived from these trials and characterize those individuals who are most likely to respond to specific treatments, thus making precision medicine "more precise."[159] Regulatory authorities recognize that in rare diseases, the evidence required for drug approval involves a trade-off between "small quantities of high-quality evidence, and large quantities of lower quality evidence."[160] In these evolving clinical trials landscape, there is an increasing need for a strong collaboration among all stakeholders, including patients and caregivers. New strategies need to balance scientific rigor with consumer-centered insights, ensuring trials are both methodologically sound and relevant to the needs and experiences of those they seek to benefit.

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DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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