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RESEARCH ARTICLE

Perampanel as precision therapy in rare genetic epilepsies

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Abstract

Objective: Perampanel, an antiseizure drug with α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor antagonist properties, may have a targeted effect in genetic epilepsies with overwhelming glutamate receptor activation. Epilepsies with loss of γ-aminobutyric acid inhibition (e.g., *SCN1A*), overactive excitatory neurons (e.g., *SCN2A*, *SCN8A*), and variants in glutamate receptors (e.g., *GRIN2A*) hold special interest. We aimed to collect data from a large rare genetic epilepsy cohort treated with perampanel, to detect possible subgroups with high efficacy.

Methods: This multicenter project was based on the framework of NETRE (Network for Therapy in Rare Epilepsies), a web of pediatric neurologists treating rare epilepsies. Retrospective data from patients with genetic epilepsies treated with perampanel were collected. Outcome measures were responder rate (50% seizure reduction), and percentage of seizure reduction after 3 months of treatment. Subgroups of etiologies with high efficacy were identified.

Results: A total of 137 patients with 79 different etiologies, aged 2 months to 61 years (mean = 15.48 ± 9.9 years), were enrolled. The mean dosage was 6.45 ± 2.47 mg, and treatment period was 2.0 ± 1.78 years (1.5 months–8 years). Sixty-two patients (44.9%) were treated for >2 years. Ninety-eight patients (71%) were responders, and 93 (67.4%) chose to continue therapy. The mean reduction in seizure frequency was 56.61% ± 34.36%. Sixty patients (43.5%) sustained >75% reduction in seizure frequency, including 38 (27.5%) with >90% reduction in seizure frequency. The following genes showed high treatment efficacy: *SCN1A, GNAO1, PIGA, PCDH19, SYNGAP1, POLG1, POLG2*, and *NEU1*. Eleven of 17 (64.7%) patients with Dravet syndrome due to an *SCN1A* pathogenic variant were responders to perampanel treatment; 35.3% of them had >90% seizure reduction. Other etiologies remarkable for >90% reduction in seizures were *GNAO1* and *PIGA*. Fourteen patients had a continuous spike and wave during sleep electroencephalographic pattern, and in six subjects perampanel reduced epileptiform activity.

Significance: Perampanel demonstrated high safety and efficacy in patients with rare genetic epilepsies, especially in *SCN1A, GNAO1, PIGA, PCDH19, SYNGAP1, CDKL5, NEU1*, and *POLG*, suggesting a targeted effect related to glutamate transmission.

KEYWORDS
genetic epilepsies, perampanel, precision therapy

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1 | INTRODUCTION

Perampanel (Fycompa) is a new generation antiseizure medication, approved by the US Food and Drug Administration and European Medicines Agency for the treatment of focal onset and generalized epilepsies in adults and children older than 4 years.[1–5] Perampanel was specifically designed in silico as a selective, noncompetitive antagonist of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA)-ionotropic glutamate receptors in the postsynaptic neurons.[1,2]

AMPA receptors enable fast excitatory synaptic transmission throughout the central nervous system, indispensable for learning, memory, and synaptic plasticity.[6,7]

Seizure generation and spreading are dependent on overactivation of AMPA receptors. Hyperactivity induced by seizures might alter posttranscriptional AMPA receptor splicing, impacting receptor desensitization and duration of excitation. Hyperactivation of AMPA receptors is highly neurotoxic, adding to secondary damage induced by seizures and epileptogenesis.[6,7]

Due to its unique mechanism of action as an AMPA receptor blocker, perampanel might be particularly effective as targeted therapy in genetic epilepsies, with overwhelming activation of the glutamate AMPA and N-methyl-D-aspartate (NMDA) excitatory receptors. This overactivation may be attributed to reduced inhibition of the γ-aminobutyric acidergic hippocampal interneurons, as seen in Dravet syndrome (due to loss-of-function variants in *SCN1A*), or to increased activation of excitatory pyramidal neurons (e.g., gain-of-function variants in *SCN2A* or *SCN8A*, loss-of-function variants in *KCNQ2*). Published small scale series suggest a higher efficacy in the subgroups of patients with Dravet syndrome[8] and Lafora disease.[9]

Likewise, higher efficacy of perampanel has been suggested in epilepsies with presumed genetic background such as Lennox–Gastaut or West syndrome.[3]

There is a special interest in epilepsy subtypes caused by genetic variants in NMDA receptors (*GRIN1, GRIN2A, GRIN2B*), as well as the extremely rare variants in AMPA receptors (*GRI*). Case reports suggest a positive effect of the anti-NMDA drug memantine on seizures and electrical status epilepticus in sleep, whereas the effect of anti-AMPA medication remains unclear.[10]

Our study aims to determine the efficacy of perampanel in rare genetic epilepsies and delineate targeted therapy approaches.

Key Points

- Perampanel may be an effective targeted therapy in genetic epilepsies with overwhelming activation of the glutamate AMPA and NMDA excitatory receptors due to either loss of inhibition in the γ-aminobutyric acidergic hippocampal interneurons, or an overactivation of excitatory pyramidal neurons
- Perampanel showed high seizure reduction and retention rates in rare genetic epilepsies
- Perampanel showed higher efficacy in certain genetic variants, including *SCN1A, GNAO1, PIGA, SYNGAP1, CDKL5, NEU1, PCDH19, POLG1*, and *POLG2*

2 | MATERIALS AND METHODS

This is a retrospective multicenter study based on anonymized chart review. Patients were recruited using the platform of the Network for Therapy in Rare Epilepsies (NETRE), a nonprofit web of pediatric neurologists and epileptologists (www.netre.de). The study was approved by the Helsinki Committee at the Wolfson Medical Center (institution review board number WOMC-0065-21).

Patients (children and adults) with epilepsy and a confirmed genetic cause who received perampanel treatment at some point during their follow-up were enrolled in the study. Collaborators collected data from the local medical records and filled a standardized anonymized case report form. The following parameters were collected: current age, age at seizure and treatment onset, type of epilepsy, seizure types, concomitant medication, name and annotation of the genetic variant, dosage of perampanel, duration of treatment, percentage of reduction in seizure frequency, and side effects. Outcome measures were defined as: (1) the responder rate, that is, percent of patients with 50% reduction in seizure frequency; and (2) the percentage of reduction in seizure frequency after 3 months of therapy. Outcome measures were calculated in the whole cohort, as well as in the patients with the most prevalent genetic etiologies (e.g., *SCN1A*).

Descriptive statistics were used to tabulate the parameters. Numeric parameters were compared using the unpaired *t*-test, whereas nominal parameters were compared using the chi-squared test. All tests were two-tailed, and a 5% tail was considered statistically significant. Data were analyzed using SPSS software (IBM, version 27).

3 | RESULTS

3.1 | Patient population

We enrolled 137 patients, 59 male (42.8%), from 25 centers in Europe, the Russian Federation, and Israel. The mean age of participants was 15.48 ± 9.9 years

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(2 months–61 years). Thirty-three patients (22.08%) were older than 18 years of age. We identified 79 different genetic etiologies across our study group. Although the majority of our cohort expressed pathogenic single nucleotide variants, our cohort also included two trisomies and eight different microdeletions. The most frequent etiology was *SCN1A*, which was encountered in 17 patients (Table 1, Figure 1A). Pathogenic variants in 10 different genes were found in subgroups of 3–6 patients (Table 1, Figure 1A), and another 10 genetic etiologies were present in subgroups of two patients each (Table 1).

Mean age at seizure onset was 3.3 ±4.5 years (2 months–25 years).

The epilepsy phenotype was diverse, including developmental and epileptic encephalopathy (including Dravet syndrome), focal epilepsies, early infantile epileptic encephalopathy, Lennox–Gastaut syndrome, epileptic encephalopathy, progressive myoclonus epilepsy, and developmental encephalopathy with epilepsy (Table 2, Figure 1B). Seizure types were likewise diverse, encompassing focal and generalized, motor and nonmotor seizures (Table 2). Most patients had more than one seizure type.

3.2 | Perampanel treatment

Treatment with perampanel was initiated at 12.7 ± 9.4 years of age (range = 1–57 years). In 17 children (12.4%), treatment was started before the age of 4 years, utilizing a compassionate use waiver. The time lag from diagnosis to treatment was 9.36 ± 7.1 years. The mean duration of treatment was 2 ± 1.78 years (1.5 months–8 years; missing data for five patients). Sixty-two patients (45.3%) were treated for >2 years (2–8 years). Five patients were lost to follow-up, and four of them passed away. The dosage of perampanel varied between 2 and 12 mg/day (mean = 6.45 ± 2.47). Perampanel was used as an add-on to 2.27 ± 2 antiseizure medications; meanwhile, only five patients (3.6%) received perampanel as monotherapy. Fifty-two patients (38%) reported various side effects, including the following: irritability (n = 20), aggressive behavior (n = 12), somnolence (n = 12), hypotension (n = 3), hypotonia (n = 2), drooling (n = 2), dizziness (n = 2), psychosis (n = 1), depression (n = 1), emotional lability (n = 1), short attention span (n = 1), ataxia (n = 1), dystonia exacerbation (n = 1), and insomnia (n = 1).

TABLE 1 Perampanel efficacy in different etiologies of genetic epilepsy.

Gene	Patients, *n*	Seizure reduction, %	Responders, *n*	Nonresponders, *n*	Seizure reduction >90%, *n*
SCN1A	17	57.94	11	6	6
TSC2	6	60.00	4	2	3
TSC1	6	40.00	2	4	1
MECP2	5	39.00	2	3	1
KCNT1	5	36.00	3	2	0
GNAO1	4	100.00	4	0	4
CDKL5	4	75.00	4	0	1
POLG1	3	66.67	3	0	1
PCDH19	3	50.00	2	1	1
NEU1	3	88.33	3	0	2
GRIN2A	3	16.67	1	2	0
TSEN54	2	87.50	2	0	1
SYNGAP1	2	70.00	2	0	1
SMS	2	35.00	1	1	0
SCN8A	2	70.00	2	0	1
POLG2	2	50.00	2	0	0
PLCB1	2	75.00	1	1	1
PIGA	2	82.50	2	0	1
MEF2C	2	25.00	1	1	0
FRRS1L	2	62.50	2	0	0
DEPDC5	2	35.00	1	1	0

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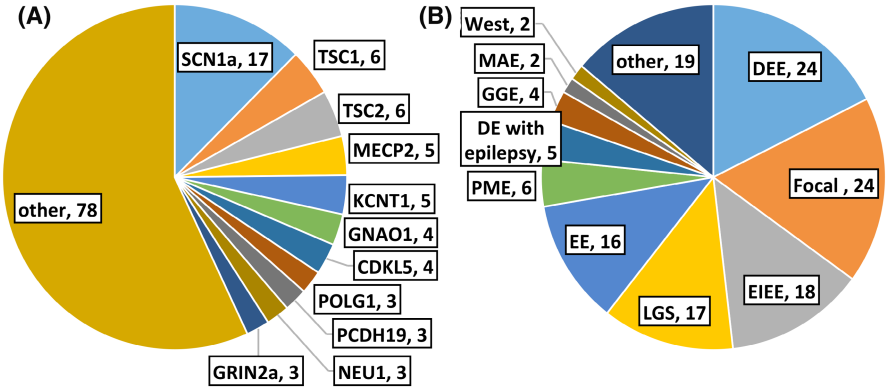

FIGURE 1 Rates of the most frequent genetic etiologies (A) and epilepsy phenotypes (B) found in our study cohort. DE, developmental encephalopathy; DEE, developmental and epileptic encephalopathy; EE, epileptic encephalopathy; EIEE, early infantile epileptic encephalopathy; GGE, genetic generalized epilepsy; LGS, Lennox–Gastaut syndrome; MAE, myoclonic atonic epilepsy; PME, progressive myoclonus epilepsy.

TABLE 2 Perampanel efficacy in different epilepsy and seizure types.

Epilepsy type	Responders, *n* (%)	Seizure type	Responders, *n* (%)
Developmental and epileptic encephalopathy	16/24 (66.7%)	Myoclonic	26/34 (76.5%)
Lennox–Gastaut syndrome	8/17 (47.1%)	Atonic	13/23 (56.5%)
Progressive myoclonus epilepsy	6/6 (100%)	Tonic	29/38 (76.3%)
Focal epilepsy	17/24 (70.8%)	Spasms	4/7 (57.1%)
Genetic generalized epilepsy	4/4 (100%)	Focal motor	34/47 (72%)
West syndrome	2/2 (100%)	Focal to bilateral tonic–clonic	16/27 (59.3%)
Myoclonic atonic epilepsy	1/2 (50%)	Generalized bilateral tonic–clonic	28/45 (62%)
Early infantile epileptic encephalopathy	16/18 (88.9%)	Focal awareness impaired	11/18 (61.1%)
Developmental encephalopathy with epilepsy	3/5 (71.3%)	Absence	16/27 (59.3%)
Epileptic encephalopathy	12/16 (75%)	Focal autonomic	7/9 (77.8%)

3.3 | Overall treatment response

The overall rate of responders was 71% (98 participants with >50% reduction in seizure frequency). The mean reduction in seizure frequency was 56.24% ± 34.69%. Sixty patients (43.5%) had >75% reduction in seizure frequency, including 38 (27.5%) with >90% reduction in seizure frequency. Ninety-three patients (67.4%) chose to continue perampanel therapy. Treatment discontinuation was due to lack of efficacy in 15 patients (10.9%), side effects in 15 patients (10.9%), and a combination of both in three patients (2.1%; missing data in 11). The most common side effect leading to discontinuation was irritability and aggressive behavior. Fourteen patients had continuous spike and wave during sleep (CSWS). Six of those patients had an improvement with perampanel treatment.

Responders and nonresponders did not differ significantly in their age at seizure onset, age at perampanel treatment initiation, time lag to treatment, dosage of perampanel (independent sample *t*-test, not significant [NS]; Table 1), gender, seizure type, and epilepsy type (chi-squared, NS). Perampanel was effective in different types of seizures and epilepsies (Table 2). There were no statistically significant differences in treatment efficacy between epilepsy subtypes (chi-squared, NS). However, the responder rate was especially high in progressive myoclonus epilepsy (100%), genetic generalized epilepsy (100%), and early infantile epileptic encephalopathy (88.9%), whereas it was lower in Lennox–Gastaut syndrome (47.1%) and myoclonic atonic epilepsy (50%; Table 2). Whereas there were no statistically significant differences in efficacy between different seizure types (chi-squared, NS), myoclonic seizures, focal motor seizures, and autonomic seizures had better response rates (Table 2).

Although responder rate did not differ significantly between distinctive genetic etiologies (chi-squared, NS), certain etiologies hold special interest.

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3.4 | SCN1A and voltage-gated sodium channels

Eleven of 17 (64.7%) patients with Dravet syndrome due to an *SCN1A* pathogenic variant were responders to perampanel treatment. The overall reduction in seizure frequency was 57.94%, and 35.29% of Dravet patients had >90% reduction in seizure frequency (five seizure-free and one with occasional seizures). Adults were more likely to be responders (69.2%, i.e., 9/13) compared to children (50%, i.e., 2/4), but the results did not reach statistical significance. Nocturnal bilateral tonic–clonic seizures were most likely to improve under perampanel treatment (three patients with this seizure type became seizure-free), whereas myoclonic seizures increased in one patient. Surprisingly, six patients were treated with lamotrigine, but there was no difference between responders (36.4%) and nonresponders (33.3%). Likewise, there was no difference in responder rate regarding other antiseizure medications including the following: benzodiazepines, valproic acid, topiramate, levetiracetam, and cannabidiol.

In addition, two patients with *SCN8A* showed a 70% improvement in seizure frequency (one seizure-free), and a patient with *SCN2A* had a marginal improvement (50% seizure reduction).

3.5 | Voltage-gated potassium channels

The improvement in seizure frequency was marginal (35%) in patients with *KCNT1*, including three of five marginal responders. One patient with *KCNQ3* became seizure-free, one patient with *KCNQ2* had a 50% response, and patients with *KCNC1* and *KCNA1* (one each) did not improve.

3.6 | Mammalian target of rapamycin pathway genes

Treatment with perampanel seemed to be more efficacious in patients with *TSC2* compared to *TSC1* variants, though results did not reach statistical significance. There was an overall 60% reduction in the seizure burden in *TSC2* (4/6 responders, including three seizure-free) versus 40% reduction in *TSC1* (2/6 responders). The effect was milder in *DEPDC5* (35% seizure reduction) and *MTOR* (50% seizure reduction).

3.7 | Progressive myoclonus epilepsy genes

All six patients with progressive myoclonus epilepsy (PME) were responders. It was especially notable that the three patients with sialidosis due to *NEU1* pathogenic variants experienced an 88.33% reduction in seizures. Another patient with *CSTB* became seizure-free, and two patients with Lafora disease due to *NHLR1* and *EPM2B* had mild improvement (60% and 50%).

3.8 | Genes related to methylation (*MECP2* and *CDKL5*)

All four patients with *CDKL5* were responders (75% reduction in seizures), with one becoming seizure-free. On the contrary, responses were seen less frequently in patients with *MECP2*, with only two of five responders.

3.9 | Polymerase gamma genes

All three patients with *POLG1* and two with *POLG2* were responders; however, seizure reduction was >90% only in one patient with *POLG1*.

3.10 | *GNAO1*

An outstanding response was found in all four patients, aged 2–7 years, with *GNAO1* pathogenic variants (three with p.Gly203Arg and one with p.Gln52Arg). Initially, all patients presented with early infantile epileptic encephalopathy, predominantly with focal motor seizures. All patients became seizure-free after initiating perampanel. One patient was on monotherapy.

3.11 | *PCDH19*

Two of the three patients with *PCDH19* were responders. A 9-year-old girl with a nonsense variant (p.Glu544Ter) became seizure-free, but the effect abated after 3 years.

3.12 | *SYNGAP1*

Both patients with *SYNGAP1* were responders. One patient with focal tonic–clonic seizures had a 90% reduction in seizures. Another patient had a 50% reduction in myoclonic absences, but eating seizures disappeared.

3.13 | *PIGA*

Two patients with *PIGA* variants and Lennox–Gastaut syndrome resistant to more than five antiseizure medications responded within days of treatment initiation with

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an 82.5% reduction in seizure frequency. Another patient with a *PIGV* variant had a less dramatic response (50% seizure reduction), but tonic seizures disappeared.

3.14 | *GRIN2A*

Patients with *GRIN2A* variants had a poor response to perampanel (6.67% overall improvement in seizures), with only one of three patients being a marginal responder. Interestingly, one of the nonresponders had a good response to memantine. All three patients with *GRIN2A* also had CSWS, which was unresponsive to perampanel.

4 | DISCUSSION

NETRE is a nonprofit web of pediatric neurologists and epileptologists created in 2005 by Gerhard Kluger (www.netre.de). The goal of this network is to exchange experiences between physicians treating patients with extremely rare epilepsies, ultimately leading to improved treatments. NETRE is currently investigating >300 disorders caused by single-gene pathogenic variants or chromosomal anomalies presenting with epileptic seizures.[11] More than 40 papers have been published by the NETRE consortium, expanding the clinical knowledge on different therapies for various etiologies.

In this study, we focused on the efficacy of perampanel in a cohort of 137 patients, encompassing 79 different genetic etiologies.

The responder rate to perampanel as add-on treatment in prospective open label as well as controlled studies is approximately 30% with a 7% seizure-free rate,[1,12] with higher efficacy seen in idiopathic generalized epilepsy.[2] Notably, our series discovered a 71% responder rate, with 27.5% patients achieving complete seizure remission or only occasional seizures. Our findings may be impacted by a recall bias toward positive results, due to previous retrospective studies reporting a considerably lower responder rate (31%–44%) and seizure-free rate (9%–17%).[3–5,13] Perampanel was found to be effective in different seizure types and epilepsy subtypes (Table 2), as previously described in the literature.[1–4,12] Although no statistically significant results were found, perampanel efficacy seemed higher in certain epilepsy subtypes (progressive myoclonus epilepsy, genetic generalized epilepsy, and early infantile epileptic encephalopathy) and types of seizures (myoclonic, focal motor, and focal autonomic).

It should be noted that these past studies suggested a targeted effect of perampanel in certain genetic epilepsies; however, these represented only small subsets of patients. We could identify certain etiology subgroups with particularly high rates of seizure reduction. However, because our study included 79 different etiologies, the differences between subgroups did not reach statistical significance.

Of patients with Dravet syndrome, 64.7% were perampanel responders, with a mean seizure reduction of 57.9%. Perampanel was seen to have similar successful effects in this highly drug-resistant epilepsy syndrome in two previously reported smaller scale series.[4,8] Response rates were higher in older patients and in those with nocturnal bilateral tonic–clonic seizures, although this finding did not reach statistical significance due to the small sample size (17 patients). Better response in older patients could also be indicative of the natural history of the disease, and not necessarily an effect of treatment. There was no difference between responders and nonresponders in antiseizure medications, but it should be noted that six patients were on lamotrigine, which also could elucidate the change in disease course in older patients.

However, the high responder rate and reduction in seizure frequency reported here are congruent with those reported for fenfluramine (68% responder rate and 75% seizure reduction)[14] and much higher than those reported for cannabidiol (43% responders and 50% seizure reduction).[15] This high efficacy of perampanel might suggest an effect on AMPA receptors that are overwhelmed by the loss-of-function of SCN1A channels in the inhibitory neurons. Additionally, two patients with *SCN8A* had a positive response, which is believed to be due to an increased activity of the channels in excitatory neurons, leading to overactivation of AMPA receptors.

A novel finding of our study is the remarkably positive effect of perampanel in patients with *GNAO1*, who had a 100% seizure reduction. Although our series comprises only four patients, this dramatic improvement warrants further investigation into the mechanism of GNAO1 and glutamate transmission. *GNAO1* loss-of-function variants cause epilepsy and neuronal hyperexcitability by deactivation of GIRK (G-coupled inward rectifying potassium) channels,[16] causing further dysfunction in glutamatergic transmission.[17]

While the number of patients with *SYNGAP1* is also small, a targeted effect of low-dose perampanel on *SYNGAP1*-related seizures has been previously demonstrated in an animal model.[18] Sullivan et al.[18] demonstrated that *SYNGAP1* haploinsufficiency causes an upregulation of AMPA receptors in the interneurons, leading to seizure generation reversible with perampanel.

In our series, both patients with *SYNGAP1*, especially with eating seizures, were responsive. Other etiologies in which perampanel was efficacious in our series were *PIGA, PCDH19*, and *CDKL5*, but not *MECP2*. We have no concrete explanation for these results, other than the effect of perampanel on general neuronal hyperexcitability present in these disorders.

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The positive effect of perampanel on cortical myoclonus in Lafora disease, as well as other types of PME, is well documented in the literature.[9,19] The mechanism of action of perampanel seems to be associated with the pathophysiology of cortical myoclonus, but not with the specific genetic etiology of PME.[20] In our series, all patients with PME were responders, but seizure reduction was more pronounced in patients with *NEU1* and *CSTB*, compared to patients with *NHLR1* and *EPM2B*.

Small series in the literature suggest good efficacy of perampanel in tuberous sclerosis complex (TSC) without differentiation between *TSC1* and *TSC2*.[4] In our series, patients with *TSC2* had a 60% reduction in seizure frequency, but seizure reduction was much lower in *TSC1*, as well as other genes related to the mammalian target of rapamycin pathway. Likewise, the effect of perampanel was modest in *GRIN2A* in the presence of CSWS, unlike the effect of the anti-NMDA medication memantine.[10]

In conclusion, perampanel is an effective therapeutic option in children and adults with rare genetic epilepsies, especially in certain genetic subgroups (*SCN1A, GNAO1, PIGA, SYNGAP1, CDKL5, NEU1, PCDH19, POLG1*, and *POLG2*), where efficacy was considerably higher, although the number of patients in each genetic subgroup was small. Further validation of our results in larger clinical cohorts, as well as in basic science studies, is needed to confirm that the effect of perampanel on glutamatergic transmission represents a true precision therapy in certain genetic epilepsies.

AUTHOR CONTRIBUTIONS

Andreea Nissenkorn: Conceptualization (equal), data curation (equal), methodology (equal), writing—original draft preparation (lead). Gerhard Kluger: Conceptualization (equal), data curation (equal), methodology (equal), writing—review & editing (equal). Susanne Schubert-Bast: Editing (supporting). Allan Bayat: Editing (supporting). Marya Bobylova: Editing (supporting). Paolo Bonanni: Editing (supporting). Berten Ceulemans: Editing (supporting). Antonietta Coppola: Review & editing (supporting). Carlo Di Bonaventura: Editing (supporting). Martha Feucht: Editing (supporting). Anne Fuchs: Editing (supporting). Gudrun Gröppel: Review & editing (supporting). Gali Heimer: Editing (supporting). Brigitte Herdt: Editing (supporting). Sviatlana Kulikova: Editing (supporting). Konstantin Mukhin: Editing (supporting). Stefania Nicassio: Editing (supporting). Alessandro Orsini: Editing (supporting). Maria Panagiotou: Editing (supporting). Milka Pringsheim: Editing (supporting). Burkhard Puest: Editing (supporting). Olga Pylaeva: Editing (supporting). Georgia Ramantani: Review & editing (supporting). Maria Tsekoura: Editing (supporting). Paolo Ricciardelli: Editing (supporting). Tally Lerman Sagie: Review & editing (supporting). Brigit Stark: Editing (supporting). Pasquale Striano: Conceptualization (supporting), Review & editing (supporting). Andreas van Baalen: Editing (supporting). Matthias De Wachter: Editing (supporting). Emanuele Cerulli Irelli: Editing (supporting). Claudia Cuccurullo: Review & editing (supporting). Celina von Stülpnagel: Editing (supporting). Angelo Russo: Conceptualization (equal), data curation (equal), methodology (equal), visualization (lead), writing—review & editing (equal).

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CONFLICT OF INTEREST STATEMENT

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