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Antiepileptic therapy approaches in *KCNQ2* related epilepsy: A systematic review

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ABSTRACT

Background: *KCNQ2* related disorders comprise both benign seizure disorders and early onset epileptic encephalopathies. Especially within the latter group, patients suffer from refractory seizures to standard antiepileptic drugs and developmental delay. Besides the hope of personalized medical approaches to treat the recently unraveled large amount of genetic channelopathies, there are sparse systematic data on treatment responses in *KCNQ2* related epilepsy in larger cohorts.

Methods: We searched PubMed using the free text term search '*KCNQ2* AND Epilepsy' and identified additional records using PubMed Medical Subject Headings (MeSH). Based on patients' clinical information about their therapy they were assigned to one of four groups: 'seizure freedom', 'responder', 'successful therapy', and 'unsuccessful therapy'.

Results: Out of 52 studies, 217 subjects were eligible for further data analyses. 133 patients were classified as 'benign' seizure disorders whereas 84 patients were classified as 'Early Onset Epileptic Encephalopathy (EOEE)'. In the 'benign' group, 92.5% of patients became seizure free while 3.8% did not respond to treatment. In contrast 65.5% of patients in the 'EOEE' group were reported seizure free, while 14.3% showed no treatment success ($p = 0.003$). Spontaneous seizure remission (without medication) was 30.1% in the 'benign' group. Phenobarbital and sodium channel blockers most often lead to seizure freedom in patients with a 'benign' course. In patients with 'EOEE' seizure freedom was more likely achieved when receiving sodium channel blockers.

Conclusions: Seizures associated with mutations within the voltage gated potassium channel *KCNQ2* are well controlled by medical treatment in patients with 'benign' courses and moderately well in patients with the 'EOEE' group. A significant number of patients in the 'benign' group may experience seizure freedom spontaneously. Phenobarbital might be considered in benign courses, while sodium channel blockers seem appropriate for both 'benign' and 'EOEE' patients.

1. Introduction

A common seizure disorder related to impaired function of potassium channels is caused by autosomal dominant mutations of the *KCNQ2* gene. These mutations lead to loss of function of the encoding cation channel *KCNQ2* (Lee, 2018). Two main types of epilepsy are associated with *KCNQ2* mutations: benign familial seizures of early infancy and 'Early Onset Epileptic Encephalopathy (EOEE)' (Miceli et al., 1993). Both syndromes may start as early as within the first days of life. Patients diagnosed with benign seizures in early infancy have an excellent prognosis regarding both seizure remission and neurodevelopment (Kaplan and Lacey, 1983). In contrast, the majority of patients with EOEE suffer from a severe phenotype comprising medical intractable seizures, intellectual disability and encephalopathic EEG. Patients with EOEE typically respond poorly to treatment and have a less favorable outcome with respect to seizure frequency and neurodevelopment. Patients with benign seizures have been reported to respond well to phenobarbital, whereas patients with EOEE are considered to respond better to phenytoin or carbamazepine (Miceli et al., 1993). However, large prospective studies with well-defined outcome variables are lacking, thus an evidence-based recommendation for a first-line therapy cannot be made so far.

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List of abbreviations

AED	Anti-Epileptic Drugs
AZA	Acetazolamide
ACTH	Adrenocorticotropic Hormone
BFNS	Benign Familial Neonatal Seizures
BFIS	Benign Familial Infantile Seizures
BFNIS	Benign Familial Neonatal Infantile Seizures
BINS	Benign Idiopathic Neonatal Seizures
BR	Potassium Bromide
BDZ	Benzodiazepines
CBZ	Carbamazepine
CLB	Clobazam
CSWS	Continuous Spike Waves during Slow Wave Sleep
CZP	Clonazepam
DZP	Diazepam
EME	Early Myoclonic Encephalopathy
EOEE	Early-Onset Epileptic Encephalopathy
ESM	Ethosuximide
EZO	Ezogabine
GBP	Gabapentin
LCM	Lacosamide
LTG	Lamotrigine
LEV	Levetiracetam
LZP	Lorazepam
MeSH	Medical Subject Headings
MDZ	Midazolam
N.f.s.	Not further specified
NZP	Nitrazepam
OXC	Oxcarbazepine
OS	Ohtahara Syndrome
PB	Phenobarbital
PHT	Phenytoin
PIR	Piracetam
PN	Pyridoxine
RTG	Retigabine
SCB	Sodium Channel Blockers
STM	Sultiame
TPM	Topiramate
VPA	Valproic acid
VGB	Vigabatrine
ZNS	Zonisamide

The *KCNQ2* gene encodes for voltage-gated potassium channels widely expressed within the brain. These channels transport potassium ions along their concentration gradient mostly out of the neuron and thus are able to generate and transmit electric signals (Biervert et al., 1998). The voltage-gated potassium channels consist of four subunits (I-IV), which in turn consist of six segments (α-helices; S1-S6). These segments are integrated into the cell membrane and are connected through intra- and extracellular amino acid chains. S4 includes a voltage-gated sensor. The ion pore is built by a loop between S5 and S6 (Biervert et al., 1998; Lerche et al., 1999; Pongs, 1992, 1999).

In the present study, we systematically reviewed studies about the treatment of patients suffering from epilepsy caused by a mutation within the *KCNQ2*-gene. We aimed to identify beneficial antiepileptic drug regimens leading to seizure reduction or seizure freedom.

2. Material and methods

2.1. Data collection procedures

We searched PubMed using the free text term search '*KCNQ2* AND Epilepsy'. Additional records were identified using PubMed Medical Subject Headings (MeSH). Two filters were applied: Epilepsy Benign Neonatal (+genetics, + therapy) and Drug Resistant Epilepsy (+genetics, +therapy). We screened abstracts for patients with a mutation within the *KCNQ2* gene and associated epilepsy. If an abstract did not provide the necessary information for including the paper in our study or rejecting it with certainty, we searched the full text of the paper. Last date to collect data from PubMed was 30th August 2017. All duplicates of articles were removed. Furthermore, we excluded papers not available in English or German. Other exclusion criteria were patients with *KCNQ2* mutations not suffering from seizures, patients without mutations in *KCNQ2* or with additional mutations to *KCNQ2* found in a single person, large deletions spanning genes besides *KCNQ2*, and lack of patients' case descriptions and response to therapy.

After screening the papers that met the inclusion criteria, we removed patients lacking clinical information regarding their treatments. Duplicates (patients who were most likely reported in more than one study) were removed. Finally, we removed all papers covering mutations with clear evidence of gain of function.

2.2. Data extraction and management

The patients' data were extracted directly from the studies and were put in an Excel spreadsheet. Based on clinical information about the therapy, patients were assigned to one of four groups: 'seizure freedom', 'responder', 'successful therapy', and 'unsuccessful therapy'. The first group 'seizure freedom' included every patient who remained seizure free for at least four weeks. The second group, 'responder', comprised all patients with a 50% or higher decrease in their seizure frequency but not reaching full 'seizure freedom' in the reported period of observation (Sprengers et al., 2017; Ben-Menachem et al., 2016; Steinig et al., 2017). All patients who did not meet the criteria for being a 'responder' or 'seizure free' but experienced a decrease in their seizures were assigned to the third group, 'successful therapy'. The last group 'unsuccessful therapy' included patients without any response to their medication.

Some papers did not report the change in a patient's seizure frequency numerically but reported the change using a descriptive phrase, e.g. 'markedly diminished'. Given the lack of literature, we decided to include those papers as well. To allow patient assignment to one of the four groups, we determined which phrases characterize which outcome group. We assigned patients to the 'seizure freedom' group' when the following phrases were used: 'successfully controlled', 'controlled (with)' and 'remission'. Patients, whose therapy was reported as 'effective', 'resolved initial seizures', leading to 'good seizure control', and 'markedly diminishing' were assigned to the group 'responder'. Those whose therapy was described as 'partially effective' were assigned to the third group, 'successful therapy'. Finally, patients whose therapy was reported as 'only mild benefit effect' and 'little response' were assigned to the fourth group, 'unsuccessful therapy'.

In addition to the therapy outcome, we extracted the following variables from the patients' descriptions: age at seizure onset, intellectual disability, sex, and the epilepsy classifications, if possible. Hereby, we wanted to confirm or refute previously described differences between the 'EOEE' and 'benign' group (Miceli et al., 1993). When a patient's epilepsy classification was not explicitly mentioned in the paper, we extrapolated it from the description of the clinical report based on the ILAE classification (Scheffer et al., 2017; Fisher et al., 2017; Fisher et al., 2014; EpilepsyDiagnosis. July 2, 2018). Furthermore, we extracted information about the mutation type (e.g. missense, truncation etc.), amino acid change, genotype analysis and whether or not the mutations are de novo. To categorize these mutations more

precisely, both Intervar (http://wintervar.wglab.org/) and the RIKEE website (http://www.rikee.org/) and database, approved by the Baylor College of Medicine Institutional Review Board, were used. RIKEE (the Rational Intervention for *KCNQ2/3* Epileptic Encephalopathy) provides interested parties with detailed descriptions of specific *KCNQ2* and *KCNQ3* mutations and their effects (Cooper, 2015). While RIKEE is a database specific to *KCNQ2/3*, the bioinformatics software InterVar provides clinical interpretations for several different genetic variants (Li and Wang, 2017). The mutations were classified into five categories by the ACMG Standards and Guidelines for the interpretation of sequence variants: pathogenic, likely pathogenic, unknown significance, likely benign, and benign (Richards et al., 2015). Patients with a benign or likely benign classification were excluded from the analysis.

2.3. Data analysis and group characteristics

The patients' characteristics are shown as means ± standard deviation of the mean, *n* being the number of patients. For the statistical analysis, the variable 'age at onset' was adjusted to the consistent unit 'days'. Syndromes were categorized as follows:

1) 'Benign familiar seizures of early infancy': BFNS, BFIS, BFNIS or BINS
2) 'EOEE': Ohtahara Syndrome, West Syndrome, CSWS, EME or "not further specified".

We analyzed whether the two groups 'benign' and 'EOEE' differed in the categories de novo, intellectual disability and sex by using a two-tailed Chi-square test with Yate's correction. Significance levels were adjusted using the Bonferroni correction. We used descriptive statistics to compare outcomes across different treatments.

3. Results

In the present study, using our search terms we found 917 studies of which 52 met the inclusion criteria. From these 52 studies, we extracted the data of 217 patients with a mutation in the *KCNQ2* gene, who were suffering from epilepsy. An overview of the search strategy as well as the inclusion and exclusion criteria is presented in Fig. 1. All of the 52 studies included in this analysis were retrospective studies (Class IV). (Glauser et al., 2013).

Table 1
Distribution of epilepsy syndromes within the 'benign' and 'EOEE' group.

EOEE (n = 84)	Benign (n = 133)
EOEE not further specified (n = 64)	BFNS (n = 91)
Ohtahara syndrome (n = 15)	BFIS (n = 19)
West syndrome (n = 2)	BFNIS (n = 12)
CSWS (n = 2)	BINS (n = 11)
EME (n = 1)	

3.1. Epilepsy classification and patients' characteristics

The group 'EOEE' included 84 patients with EOEE, Ohtahara Syndrome, West Syndrome, CSWS, EME or patients whose epilepsy classification was not further specified. Patients with the epilepsy classifications 'benign' included 133 patients with BFNS, BFIS, BFNIS or BINS (Tables 1 and 2). For detailed patients' characteristics, see Table 2.

3.2. Intellectual disability

In the 'EOEE' group 97.5% of patients were described to have an ID. Interestingly, even 20.5% of patients assigned to the 'benign' group were reported to have an ID (Table 2).

3.3. Genetics

Mutations occurred de novo in 25.6% of patients assigned to the 'benign' group and in 82.6% of patients assigned to 'EOEE' ($p < .001$). The following mutation types were found in the 'benign' group: missense 63.9%, frameshift 13.5%, deletion 12.8%, splice site 6.0%, single

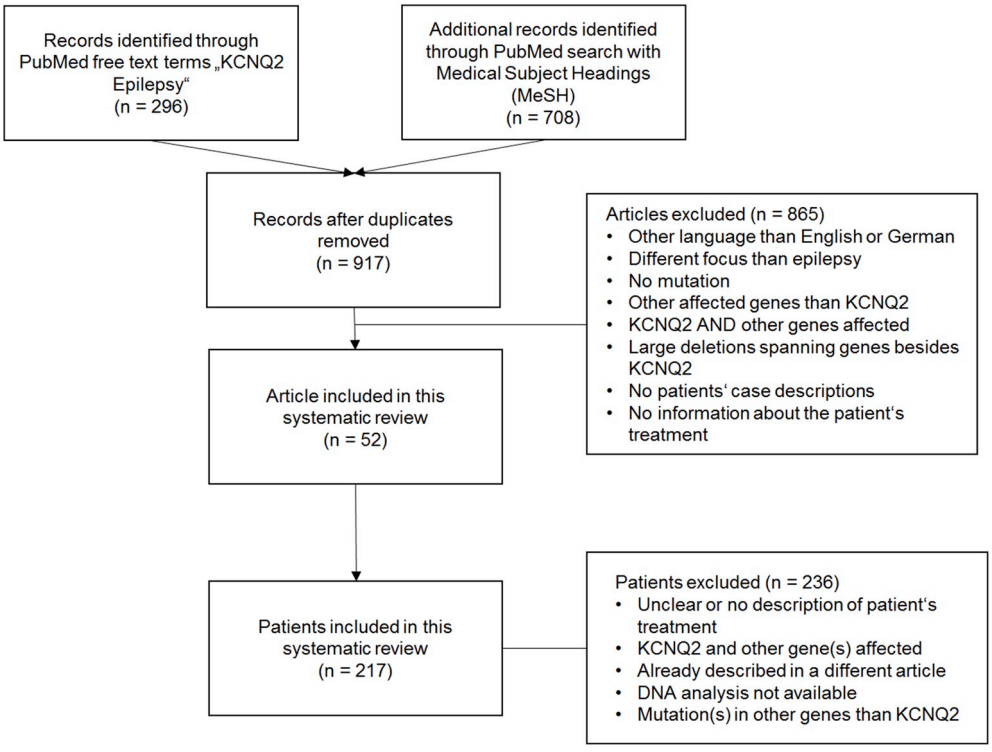

Fig. 1. Selection criteria for included articles. Overview of the search strategy and of the inclusion and exclusion criteria.

Table 2
Patients' characteristics.

	All	benign'	‚EOEE'	p values
Type of mutation				
missense	n = 167 (77%)	n = 85 (63.9%)	n = 82 (97.6%)	
frameshift	n = 18 (8.3%)	n = 18 (13.5%)		
splice site	n = 8 (3.7%)	n = 8 (6.0%)		
deletion	n = 19 (8.7%)	n = 17 (12.8%)	n = 2 (2.4%)	
single AS deletion	n = 3 (1.4%)	n = 3 (2.3%)		
truncation	n = 2 (0.9%)	n = 2 (1.5%)		
De novo*				p < .001
yes	n = 77 (52.4%)	n = 20 (25.6%)	n = 57 (82.6%)	
no	n = 70 (47.6%)	n = 58 (74.4%)	n = 12 (17.4%)	
Intellectual disability*				p < .001
yes	n = 95 (61.3%)	n = 15 (20.5%)	n = 79 (97.5%)	
no	n = 60 (38.7%)	n = 58 (79.5%)	n = 2 (2.5%)	
Sex				p = 0.257
f	n = 103 (55.4%)	n = 69 (59.0%)	n = 34 (49.3%)	
m	n = 83 (44.6%)	n = 48 (41.0%)	n = 35 (50.7%)	
Age at onset (d) X (range) average ± standard deviation				
all	20.0 (1–1399)	15.5 (1–183)	9.3 (1–183)	
< 30 d	2.9 (1–30)	4.3 (1–30)	2.4 (1–14)	
31–100 d	72.1 (46–91)	73.1 (56–91)	68.5 (46–91)	
100–200 d	140.7 (107–183)	139.8 (107–183)	142.4 (122–183)	
> 200 d	1399		1399	
Observation period (months)				
	178 (0.8–936)	98 (0.8–936)	80 (0.9–444)	
	102.7 ± 141.5	135.6 ± 172.2	62.2 ± 72.5	

The table shows differences in the distribution of mutations, *De novo* mutations, intellectual disability, sex, age at onset, and period of observations between the groups 'benign' and 'EOEE.
*Significance level is $p < 0.05$.

amino acid deletion 2.3% and truncation 1.5%. In the 'EOEE' group, two types of mutation were identified: missense 97.6% and deletion 2.4% (Table 2). The distribution of missense mutations is depicted in Fig. 2. Regarding the distribution of mutations, no significant correlation between treatment response or phenotype was found.

3.4. Seizure outcome and response to AED

We compared treatment outcomes for each of the two groups. Patients were treated with either one medication (monotherapy) or a combination of different medications (polytherapy). The reported medications included AEDs (n = 19) and 'others' (ACTH, corticosteroids, folinic acid, ketogenic diet, low glycemic index treatment, lidocaine, and pyridoxine).

3.5. Seizure outcome 'benign' group

In the 'benign' group (n = 133 patients) 92.5% of patients became seizure free while 3.8% showed no response to any treatment. Seventy-four patients became seizure free with a monotherapy, while four remained unsuccessful. Eleven patients, who were treated with a polytherapy, became seizure free while two showed no effect. When considering monotherapy in patients within the 'benign' group, the majority of treatments included phenobarbital (n = 65, 46.1%), sodium channel blockers (n = 21, 14.9%) or valproic acid (n = 13, 9.2%), (Fig. 3a). Sodium channel blockers included CBZ, OXC, LTG, and PHT. In the majority of patients, the administered AEDs lead to seizure freedom: phenobarbital 73.8%, sodium channel blockers 90.5% and valproic acid 76.9% respectively. There was no statistically significant difference between these three drugs (Fig. 3b). In 40 patients (30.1%), seizure cessation occurred spontaneously without medication. In the 'benign' group the majority of polytherapy treatments leading to seizure remission included PB (n = 10, 90.9%).

3.6. Seizure outcome 'EOEE' group

In the 'EOEE' group (n = 84), 65.5% of patients were reported seizure free, while 14.3% showed no treatment success. Out of 76 patients treated with a monotherapy, 48 became seizure free while 12 remained unsuccessfully treated. When considering monotherapy in patients within the 'EOEE' group, the majority of treatments included sodium channel blockers (n = 45, 18.7%), 'others' (n = 40, 16.6%) and phenobarbital (n = 35, 14.5%) (Fig. 4a). The distribution of seizure medication of patients achieving seizure freedom was as follows: 37.8% out of all treatment trials with sodium channel blockers, 26.3% out of all treatment trials with valproic acid and 33.3% out of all treatment trials with levetiracetam lead to seizure freedom. Sodium channel blockers included CBZ, OXC, LTG, LCM, and PHT. The treatment trials with phenobarbital were primarily unsuccessful: 8.6% lead to seizure freedom while 74.3% showed no effect at all. Out of all mono-therapeutic treatment trials with retigabine, 14.3% led to seizure freedom while 71.4% showed no effect.

Out of 26 patients treated with a polytherapy, 20 became seizure free and zero patients showed no success at all. Two patients exhibited spontaneous seizure reduction without medication. There were no remarkable differences between types of polytherapy in treatment success.

4. Discussion

In the present study, we aimed to determine the most successful treatments of *KCNQ2* related seizures in both 'benign' and 'EOEE' cases. Therefore, we performed a systematic review and final analysis of 217 subjects harboring *KCNQ2* mutations and reported treatment approaches. In the 'benign' group, one third of all events leading to seizure freedom happened spontaneously (30.1%). This is in line with the known course of the disease. In general, patients with a mutation in *KCNQ2* suffering from BFNE become seizure free spontaneously in the first month of life or between the sixth – 12th. Month of life (Miceli et al., 1993). Our analysis shows that PB was the most commonly used monotherapy, followed by sodium channel blockers and led to seizure cessation in the majority of patients. The broad use of PB (Fig. 3a) is most likely attributed to the fact that PB is supposed to be the standard of care therapy in neonatal seizures. In addition, previous research on *KCNQ2* related disorders showed that the majority of children suffering from *KCNQ2* BFNE remain seizure free using PB (Miceli et al., 1993). However, one should consider that patients with a benign phenotype remit spontaneously during the course of the disease. Hence, we cannot determine whether the improvement in seizure frequency was due to the medication or occurred spontaneously due to the benign course. Sodium channels blockers lead to seizure freedom in about 90% of treated patients. Among sodium channel blockers, CBZ most often led to seizure freedom (100%). (Sands et al., 2016). This finding should be considered with caution because CBZ was only administered to 12 patients. However, it is in line with recent studies proposing CBZ as the 'drug of choice' in benign familial neonatal seizures. Furthermore, these studies prefer CBZ to PB because of fewer side effects such as sedation and hypotension (Vilan et al., 2017). Other sodium channel blockers exhibit distinct disadvantages i.e. the adverse event profile of phenytoin (purple glove syndrome, cerebellar toxicity, and cardiac arrhythmias) or long-lasting dosing increments of lamotrigine.

Thus, it might be reasonable to use sodium channel blockers such as CBZ or OXC as a first line therapy in patients with benign cases of *KCNQ2* related seizures.

As known, 'EOEE' patients have a worse response to treatment than

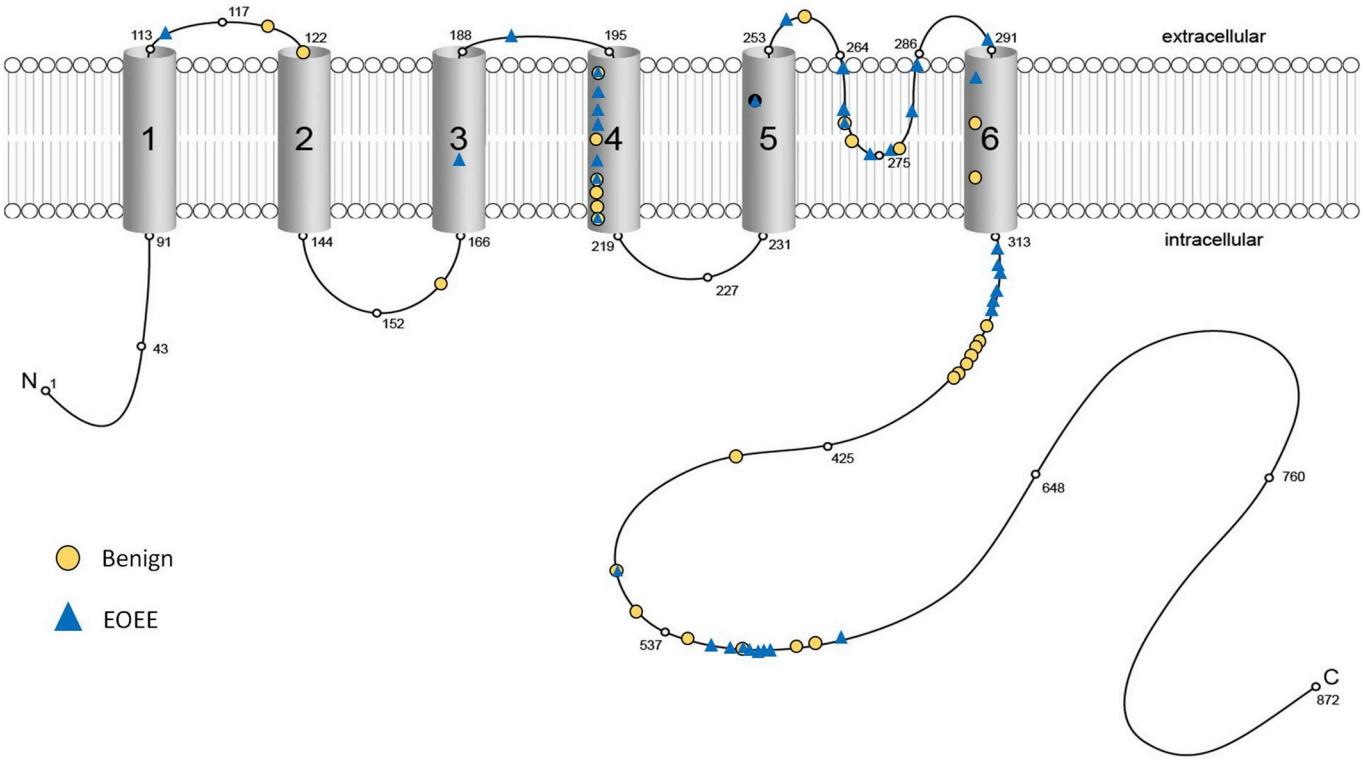

Fig. 2. Distribution of missense mutations within the *KCNQ2* polypeptide chain. The triangle symbols depict the missense mutations of patients classified as 'EOEE' whereas the circle symbols represent the 'benign' group.

'benign' patients do (Miceli et al., 1993). Specifically, many 'EOEE' patients show multiple daily seizures resistant to AEDs. In our study, the majority of therapy approaches with a monotherapy (61.6%) did not lead to any improvement in seizure frequency in the 'EOEE' group. Especially therapy approaches with PB were primarily ineffective. Since as few as 8.6% out of all therapy approaches leading to seizure freedom while 74.3% showed no effect at all, its administration cannot be recommended for patients in the 'EOEE' group.

Sodium channel blockers improved patients' seizure frequency in the 'EOEE' group most likely: 37.7% out of all therapy approaches lead to seizure freedom. However, SCB were not clearly superior to LEV or VPA (Fig. 4b) indicating that the latter AEDs might be considered in patients who failed to respond to SCB.

The finding that retigabine opens the Kv7 potassium channel sparked a lot of interest in its use as an AED in patients with a *KCNQ2* mutation (Barrese et al., 2010; Gunthorpe et al., 2012). After its approval by the US Food and Drug Administration (FDA) in 2011, retigabine was introduced as an adjunctive therapy in adults with partial-onset seizures (Porter et al., 2012). Although retigabine's seemed to be an effective treatment (Weckhuysen et al., 2013), its prescription was questioned as some patients developed side effects such as blue discoloration of skin and retina (Clark et al., 2015; Garin Shkolnik et al., 2014). In 2017, the company withdrew retigabine from all markets 'due to very limited use and declining numbers of patients initiating therapy on the drug' (Glaxosmithkline. Advance, 2017). In our analysis, we could not detect a benefit of retigabine compared to other drugs such as SCB. In one patient, therapy with retigabine even led to a deterioration of his condition (increased paroxysmal events, prolonged apneas, and severe sedation). (Mulkey et al., 2017).

Sodium channel blockers seem to improve seizure frequency in both groups. SCB impair the conduction of sodium ions through the channels, reduce conduction velocity and thus, block the development of seizures (Brodie, 2017; Arya and Glauser, 2013; Abdelsayed and Sokolov, 2013). Furthermore, it was shown that voltage-gated sodium channels and KCNQ potassium channels co-localize at the neuronal membrane (Pan et al., 2006). Therefore, a modulating effect of SCB on both channels, sodium and potassium, has been suggested (Pisano et al., 2015).

Interestingly, PB was more effective among patients with a benign phenotype than those with an 'EOEE' phenotype. We found no plausible explanation from basic science experiments for this discrepancy in the current literature.

4.1. Intellectual disability

As expected, the vast majority of patients assigned to the 'EOEE' group had documented intellectual disability. In general, patients with 'benign' courses reveal a good neurodevelopment. However, in our review, 20.5% of patients assigned to the 'benign' group were reported to have an intellectual disability. One possible explanation is that patients were incorrectly classified as having a benign course (Hirfanoglu et al., 2007). One should consider that some overlap between 'benign' and 'EOEE' courses might exist. In addition, seizure freedom might not alone qualify to be considered a 'benign' course as intellectual disability and additional comorbidities have a significant impact on patients' and caregivers' perception of quality of life (Baca et al., 2011). In addition, it has been shown that distinct epileptic parameters as seizure frequency and EEG abnormalities do not necessarily correlate with the degree of intellectual and behavioral disturbances in other epileptic channelopathies as *SCN1A* related seizure disorders (Dravet-syndrome) (Nabbout et al., 2013). However, the latter relations have not been studied in *KCNQ2* related seizure disorder.

4.2. Genetics

In the cohort investigated in this study, 25.6% of patients classified as 'benign' were reported to have de novo mutations, a higher percentage than previously found (Miceli et al., 1993). In contrast, the majority of patients with 'EOEE' (67.9%) carry de novo mutations (only 14.3% out of patients' mutations were inherited), which was in line

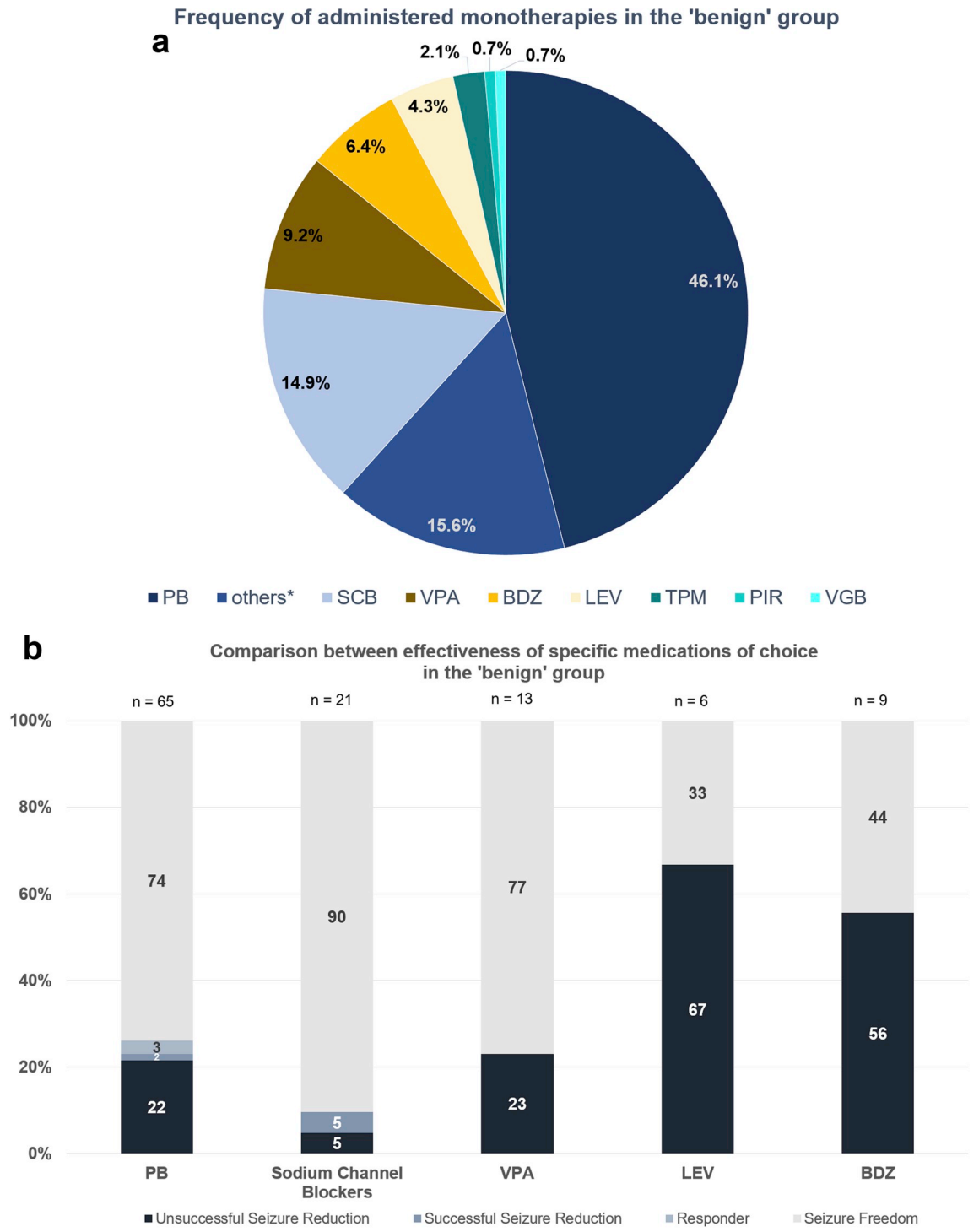

Fig. 3. a)**Frequency of administered monotherapies in the 'benign' group.** Sodium channel blockers included CBZ, LTG, OXC and PHT. Benzodiazepines included CZP, DZP and MDZ. Others included lidocaine, folinic acid and pyridoxine. b)**Comparison between effectiveness of specific medications of choice in the 'benign' group.**

Fig. 3a, b and Fig. 4a, b: When mentioned, in each figure and in the text "n" refers to the number of therapy approaches rather than the number of patients because any patient may have undergone one or several therapy approaches. A therapy approach may consist of treatment with a specific drug or treatment with a combination of drugs. For example, if a patient was first unsuccessfully treated with AED, then switched to a different drug, which resulted in seizure freedom for 6 months, he would have gone through two therapy approaches.

with prior research. However, selection bias caused by our inclusion criteria of publications, which had to mention treatment options, has to be considered.

4.3. Personalized therapy in epilepsy genetics

The fast-growing knowledge of genetic epilepsies raises hope of personalized therapy approaches once a genetic cause is established. However, given the large amount of unraveled monogenetic epileptic

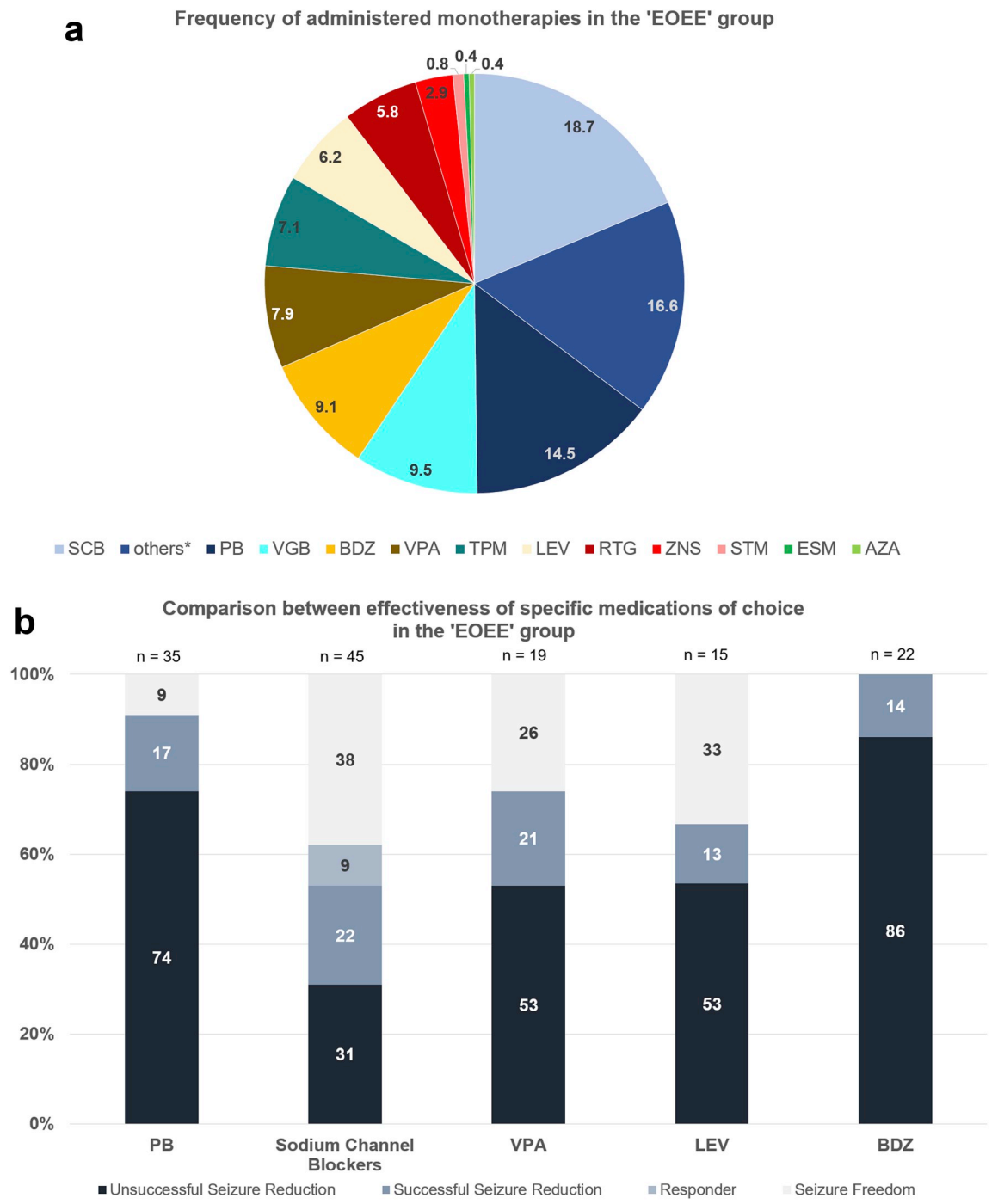

Fig. 4. a)**Frequency of administered monotherapies in the 'EOEE' group.** Sodium channel blockers included CBZ, LCM, LTG, OXC and PHT. Benzodiazepines included CLB, CZP, DZP, MDZ, NZP and BDZ not further specified. 'Others' included ACTH, folinic acid, hydrocortisone, ketogenic diet, low glycemic index treatment, lidocaine, prednisolone and pyridoxine. b)**Comparison between effectiveness of specific medications of choice in the 'EOEE' group.**
Fig. 3a, b and Fig. 4a, b: When mentioned, in each figure and in the text "n" refers to the number of therapy approaches rather than the number of patients because any patient may have undergone one or several therapy approaches. A therapy approach may consist of treatment with a specific drug or treatment with a combination of drugs. For example, if a patient was first unsuccessfully treated with AED, then switched to a different drug, which resulted in seizure freedom for 6 months, he would have gone through two therapy approaches.

disorders within the last decade only a comparably low yield of personalized therapy options has been published (i.e. avoidance of sodium channel blockers in *SCN1A* associated epileptic disorders (Jensen et al., 2014) and the preference of these agents in early but not late onset *SCN2A* associated epilepsy (Wolff et al., 2017)). Instead, new approaches directly targeting ion channels by i.e. small molecules or change gene expression using targeted antisense nucleotides might be promising candidates.

4.4. Classification of evidence

All of the 52 studies included in this analysis were retrospective (Class IV) studies. Thus, according to the classification level of evidence of the International League Against Epilepsy (ILAE) (Glauser et al., 2013), the results of the present study might be stated as level D of evidence suggesting potential effect of phenobarbital and sodium channel blockers in *KCNQ2* related epileptic disorders.

4.5. Limitations

Our study may have several limitations, which should be considered when interpreting our results. Firstly, some of the studies included in our analysis did not report seizure frequency and outcomes in precise numeric terms but using vague descriptive phrases. Therefore, we were forced to base assignment to the four groups (unsuccessful, successful, responder, seizure freedom) on these less precise phrases.

Secondly, it is plausible that pooled data are at risk of causing a significant variability of quality. Thirdly, the observation periods -if documented at all- varied, making it difficult to compare different treatment outcomes. Fourthly, one disadvantage was the retrospective design of the study we were forced to use. A systematic review does not provide data on a longitudinal course. Hence, this supports other prospective study designs in order to investigate the treatment responses in patients with genetic epilepsies. A meta-analysis with individual patient data (IPD-analysis) might be more appropriate in genetic epilepsies as this approach allows a more longitudinal view on patients and thus gives a better reflection of the course of the disease i.e. seizure reduction by distinct AEDs (Thomas et al., 2014). Nevertheless, the gold-standard of investigating treatment responses are prospective randomized controlled trials with an appropriate observation period. Fifthly, the study did not control for other variables which may affect seizure frequency and response to therapy, e.g. patients' origin, nutrition, or their compliance. Sixthly, we cannot determine whether the improvements in seizure frequency in both groups ('benign' and 'EOEE') were due to the medication or occurred spontaneously due to the natural course of the disease. Finally, the ILAE advises against the use of the term 'benign' as it implies a good outcome for the patients even though some patients develop ID, developmental delay or movement disorders (Scheffer et al., 2017). Instead, they recommend the terms 'pharmacoresponsive' or 'self-limited'. Nevertheless, we decided on the term 'benign' because not all patients included in our study were equally pharmacoresponsive and not all had a self-limiting course. In addition, the vast majority of studies on *KCNQ2* related epilepsies still uses the term. Seventhly, as the EEG has not been reported in all cases, some patients were classified according to their seizure type only.

5. Conclusions

First of all, this review reveals the use of a broad spectrum of AEDs to treat seizures in *KCNQ2* related epilepsy. The most common drugs used were PB in 'benign' phenotypes and both, PB and sodium channel blockers, in 'EOEE' phenotypes. Our study provides additional support for using PB and CBZ in patients with *KCNQ2* mutations assigned to the 'benign' group. Furthermore, sodium channel blockers such as CBZ, PHT and LCM seem to improve seizure frequency in the 'EOEE' group. To date, there is a lack of randomized controlled studies, making a reliable suggestion for a targeted treatment difficult. Future studies should use clearly defined outcome variables (i.e. proportions of seizure free patients of proportions of patients revealing more than 50% seizure reduction) enabling a more precise comparison of treatments. Furthermore, defined periods of observations, e.g. a minimum of six months, preferable 12 months should be achieved.

Conflicts of interest

All authors report no conflict of interest, which is related to the contents of this study.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejmg.2019.02.001.

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