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Influence of new versus traditional antiepileptic drugs on course and outcome of status epilepticus

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ABSTRACT

Purpose: New antiepileptic drugs (AEDs) are increasingly applied in second-line therapy of status epilepticus (SE). In our study, we analyzed the impact of the choice of second-line AEDs on the course and prognosis of SE.
Methods: This retrospective single- center study used data of an 8 year cohort of SE in adults from 2007 to 2014. Based on the year of market introduction with a cutoff at 1990, we classified AEDs as traditional or new. Prescription pattern associated differences in prognosis were measured through univariate and multivariable analysis of 3 endpoints: occurrence of refractory SE (RSE), functional outcome in survivors to discharge (*good*: mRS at discharge < 3 or identical to admission mRS; otherwise *poor*), and in-hospital mortality.
Results: From 362 SE episodes during the study period, 222 episodes were included into the study, among those 150 episodes treated with new and 72 with traditional AEDs. Use of new AEDs increased during the study period. After adjustment for confounders, treatment with new AEDs was on the one hand associated with higher rate of RSE occurrence (OR 1.95, 95 % CI 1.05–3.62, p = 0.03), but, on the other hand, also with better functional outcome at discharge (OR 2.64, 95 % CI 1.16–6.00, p = 0.02), while it was not an independent predictor of in-hospital mortality (OR 0.88, 95 % CI 0.33–2.33, p = 0.80).
Conclusion: Our observation that new AEDs may be associated with a higher rate of RSE development and relatively better functional outcome when adjusted for the premorbid mRS needs confirmation in prospective studies.

1. Introduction

Status epilepticus (SE) is a frequent neurological emergency with an incidence of 16–36/100,000 [1,2]. The prognosis of SE is largely determined by unmodifiable patient characteristics like age, a history of previous seizures, the patient's premorbid functional status, the seizure semiology, EEG patterns, and particularly the etiology underlying the SE [3–8]. However, prolonged SE duration also contributes to poor prognosis, mirrored by mortality rates of 25 % in refractory SE as compared to approximately 10 % in non-refractory SE [9,10]. Thus, treatment aims at aborting seizure activity as quickly as possible. While first-line treatment with benzodiazepines is well-established, there is only limited evidence regarding the further steps of SE therapy. In clinical practice, a growing number of antiepileptic drugs (AEDs) with different modes of action are applied at this stage [11]. In the last decades, there was a switch in prescription patterns in favor of so-called new AEDs [12], and the question arises whether the choice of new second-line therapeutic strategies has a benefit concerning clinical course and outcome in SE. The Established Status Epilepticus Treatment Trial (ESETT) [13] will help clarify this issue, but the results are still pending. Recent studies related the use of newer AEDs at some point during an SE episode to lower rates of successful seizure cessation and worse overall prognosis [12,14]. The aim of the present study was to examine the influence of new vs traditional AEDs when used as second-line therapy on course and outcome of SE.

Abbreviations: SE, status epilepticus; RSE, refractory status epilepticus; AED, antiepileptic drug; STESS, Status Epilepticus Severity Score; mRS, modified Rankin Scale; OR, Odds Ratio; CI, confidence interval; ICU, intensive care unit

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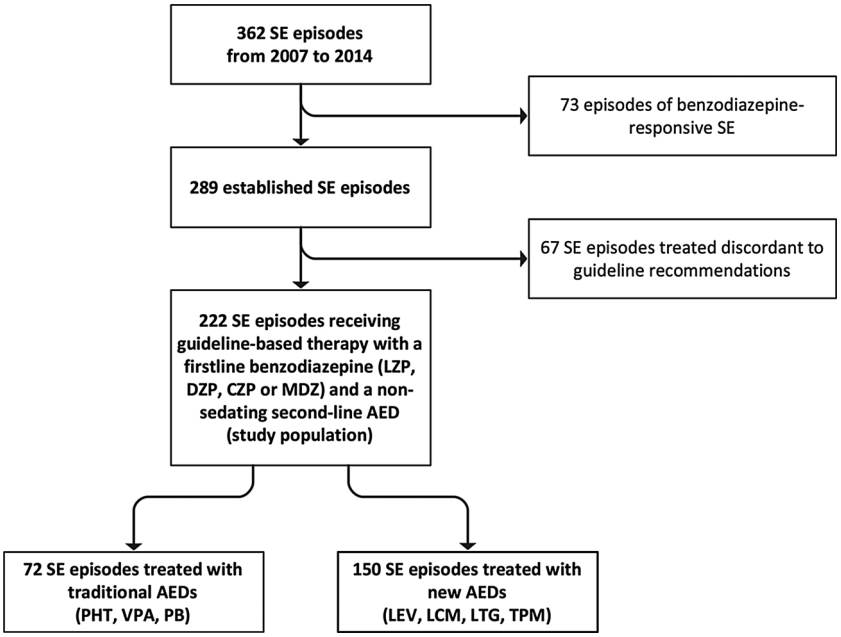

Fig. 1. Flow chart of the study cohort.
Abbreviations: SE status epilepticus, AED antiepileptic drug, LZP lorazepam, DZP diazepam, CZP clonazepam, MDZ midazolam, PHT phenytoin, VPA valproic acid, PB phenobarbital, LEV levetiracetam, LCM lacosamide, LTG lamotrigine, TPM topiramate.

2. Methods

2.1. Definition of new and traditional AEDs

According to the year of market introduction before or after 1990, levetiracetam, lacosamide, lamotrigine, and topiramate were defined as new AEDs while phenytoin, valproic acid, and phenobarbital were classified as traditional AEDs [15,16].

2.2. Study population

SE was defined as clinical and/or electroencephalographic evidence of seizure activity for ≥ 5 min or as series of seizures with incomplete interictal clinical recovery, following its operational definition [17,18] and in line with previous studies [7,19]. Only episodes in which patients (aged 18 years or older) failed to respond to benzodiazepines and required second-line medication (= established SE) were included. We excluded all cases in which the sequence of the first two SE treatment steps was other than an intravenous benzodiazepine followed by a second-line AED [20,21]. Episodes were categorized as treated with new vs traditional AEDs based on whether they received a new or traditional AED as the first medication after initial benzodiazepines.

An SE episode was defined as refractory when seizures persisted clinically or on EEG after application of a first-line benzodiazepine and a second-line AED therapy [22]. SE secondary to hypoxic encephalopathy was excluded from this study.

The Status Epilepticus Severity Score (STESS) was calculated for all episodes [23]. SE etiologies that can lead to death irrespective of SE were defined as potentially fatal, as proposed by Rossetti and coworkers [3]. We assessed functional status using the modified Rankin Scale [24].

2.3. Outcome definitions

Outcome measures were (i) refractoriness to first- and second-line treatment, (ii) functional outcome at discharge in survivors, and (iii) death during hospital stay. Functional outcome was measured by the comparison of the modified Rankin Scale score (mRS) at time of hospital discharge with the premorbid mRS. Good functional outcome was defined as either unchanged mRS during hospital stay (i.e., complete recovery) or as an mRS at discharge < 3.

2.4. Statistical analysis

Statistics were performed using IBM SPSS Statistics 22.0 (http://www.spss.com). Illustrations were created with GraphPad Prism 7.0 (http://www.graphpad.com) and rawgraphs 2.0 (https://rawgraphs.io). Proportions were compared using Pearson's Chi^2 test, continuous variables were compared using the Mann-Whitney U test. Two-sided p values of less than 0.05 were considered statistically significant. Variables showing significant differences or a statistical trend ($p \leq 0.1$) in the univariate comparison between groups were considered candidate covariates for multivariable analyses using binary logistic regression. Instead of integrating STESS as covariate in multivariable analyses, we used its single parameters when these showed significant difference in univariate analyses. Application of new AEDs as a variable was forced into the models in case of lacking association with the respective outcome upon univariate analysis.

3. Results

We identified 362 SE episodes in our databases in the period from 2007 to 2014. After exclusion of 73 benzodiazepine-responsive episodes and 67 episodes not receiving guideline-concordant therapy in terms of medication sequence (33 episodes not prescribed an intravenous benzodiazepine as first-line treatment and 34 episodes receiving anaesthetics before initiation of treatment with non-sedating AEDs), 222 SE episodes in 182 patients remained for analysis. Of these, 150 cases were treated with new AEDs (146 levetiracetam, 1 topiramate, 2 lacosamide, 1 lamotrigine) and 72 cases received traditional AEDs (58 valproic acid, 12 phenytoin, 2 phenobarbital; Figs. 1 and 3). During the study period, the use of new AEDs increased while the prescription rate of traditional AEDs declined (Fig. 2).

Univariate analyses revealed that generalized convulsive SE episodes were treated significantly more often with traditional AEDs (54.2 % vs 39.3 %, p = 0.04), while simple partial and complex partial

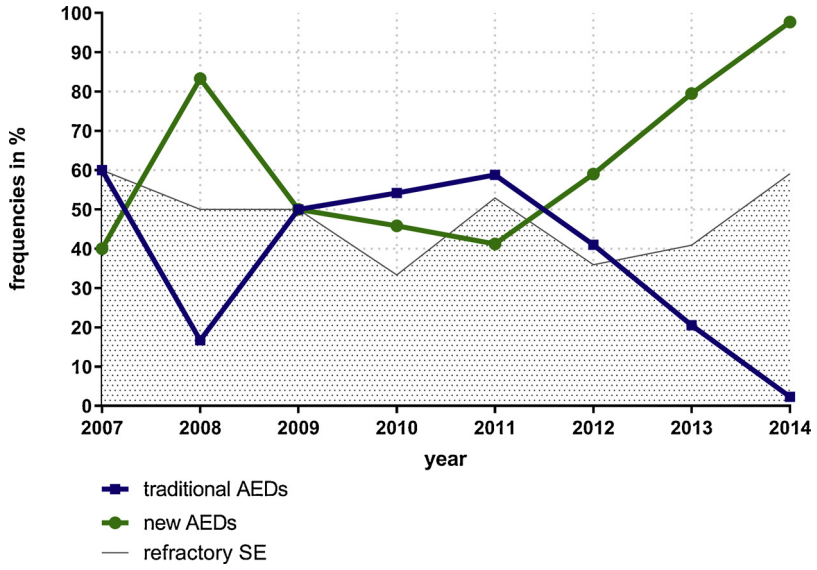

Fig. 2. Evolution of prescription pattern of new and traditional AEDs and the refractoriness rate over the study period.
Abbreviations: AED antiepileptic drug, SE status epilepticus.

episodes received significantly more often new AEDs (54.7 % vs 36.1 %, p = 0.01). The distribution of STESS values differed significantly between the cohorts (p = 0.003), although the median STESS was identical. Demographics, etiology, level of consciousness, treatment details, and outcomes showed no significant difference between the two treatment groups (Table 1).

On unadjusted comparison, the application of new AEDs was not significantly associated with the occurrence of RSE (52.0 % vs 40.3 %, p = 0.10), good functional outcome at discharge (58.7 % vs 50.0 %, p = 0.23), and in-hospital mortality (11.3 % vs 11.1 %, p = 0.96).

The results of the univariate analyses that were used for identification of covariates for the multivariable models are detailed in supplementary Tables 1–3. After adjustment for the respective confounders, the use of new AEDs was an independent predictor for progression into RSE (odds ratio [OR] 1.95, 95 % confidence interval [CI] 1.05–3.62, p = 0.03) and good functional outcome at time of discharge (OR 2.64, 95 % CI 1.16–6.00, p = 0.02). In-hospital mortality was not influenced by whether patients received new or traditional AEDs (OR 0.88, 95 % CI 0.33–2.33, p = 0.80) (Table 2).

For illustration of distribution of premorbid mRS and functional outcome at discharge in the two treatment groups see Fig. 4.

4. Discussion

In the present study, we compared the impact of application of new vs traditional AEDs for second-line treatment on the course and outcome of SE. In line with previous reports, we observed a substantial increase of prescription of new AEDs during the study period. The main findings were (i) that use of new AEDs was an independent predictor for the occurrence of RSE, but (ii) not for in-hospital mortality, while, paradoxically in light of (i), (iii) their application was related to better functional outcome at discharge. These results, however, need to be interpreted in the context of the methodological limitations inherent in the retrospective single-center study design without data on timing and

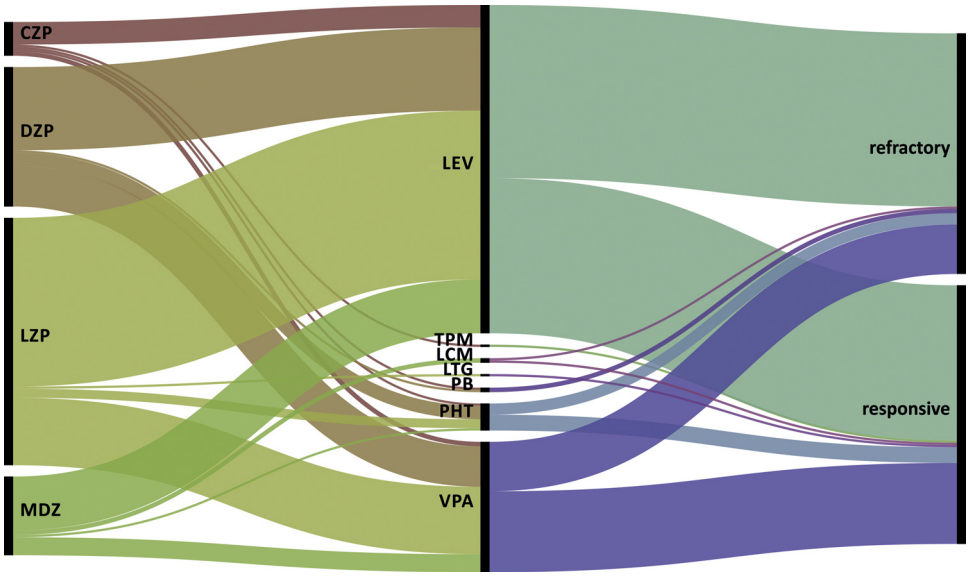

Fig. 3. Flow diagram of first- and second-line therapy and treatment-refractoriness.
Abbreviations: LZP lorazepam, DZP diazepam, CZP clonazepam, MDZ midazolam, PHT phenytoin, VPA valproic acid, PB phenobarbital, LEV levetiracetam, LCM lacosamide, LTG lamotrigine, TPM topiramate.

Table 1
Association of prescription pattern with demographics, SE characteristics, and outcome.

	Total cohort (n = 222)	Traditional AEDs (n = 72)	New AEDs (n = 150)	p-value
Demographics				
Female gender	121 (54.5)	42 (58.3)	79 (52.7)	0.43
Age on admission, years	71 (60 – 77)	72 (61 – 78)	71 (59 – 77)	0.50
Age ≥ 65 years	146 (65.8)	50 (69.4)	96 (64.0)	0.43
Premorbid mRS	3 (1 – 4)	3 (2 – 4)	3 (1 – 4)	0.11
Status epilepticus characteristics				
STESS	3 (2 – 4)	3 (2 – 4)	3 (2 – 4)	**0.003**
STESS ≥ 3	129 (58.1)	52 (72.2)	77 (51.3)	**0.003**
Etiology				
History of seizures	128 (57.7)	36 (50.0)	92 (61.3)	0.11
Potentially fatal etiology	69 (31.1)	23 (31.9)	46 (30.7)	0.85
Level of consciousness				
Stuporous or comatose	119 (53.6)	45 (62.5)	74 (49.3)	0.07
Worst seizure type before initiation of treatment				
Generalized convulsive	98 (44.1)	39 (54.2)	59 (39.3)	**0.04**
NCSE in coma	16 (7.2)	7 (9.7)	9 (6.0)	0.32
Simple partial or complex partial	108 (48.6)	26 (36.1)	82 (54.7)	**0.01**
Treatment				
Continuous intravenous anesthetic drugs	58 (26.1)	20 (27.8)	38 (25.3)	0.70
Number of AEDs	3 (1 – 5)	2 (1 – 5)	3 (1 – 5)	1.00
Outcome				
Refractoriness to 1st- and 2nd-line medication	107 (48.2)	29 (40.3)	78 (52.0)	0.10
In-hospital mortality	25 (11.3)	8 (11.1)	17 (11.3)	0.96
Good short-term outcome	124 (55.9)	36 (50.0)	88 (58.7)	0.23

Values are n (%) or median (IQR, interquartile range, 25th to 75th percentile). Proportions were compared using Pearson's Chi^2 test, continuous variables were compared using the Mann-Whitney U test. Statistically significant values ($p < 0.05$) are expressed in bold. Abbreviations: STESS Status Epilepticus Severity Score, mRS modified Rankin Scale, NCSE nonconvulsive status epilepticus, SE status epilepticus, AED antiepileptic drug.

Table 2
Multivariable logistic regression models for in-hospital mortality, good functional outcome at discharge, and development of refractory status epilepticus.

	Odds Ratio	95 % Confidence interval	p-value
Refractoriness to 1st- and 2nd-line medication			
New AEDs	1.951	1.052 – 3.619	**0.03**
Age ≥ 65 years	0.678	0.376 – 1.223	0.20
Potentially fatal etiology	1.518	0.829 – 2.781	0.18
Stuporous or comatose	1.668	0.840 – 3.310	0.14
NCSE in coma	3.536	0.915 – 13.660	0.07
Simple partial or complex partial SE	0.741	0.369 – 1.492	0.40
In-hospital mortality			
New AEDs	0.880	0.333 – 2.329	0.80
Potentially fatal etiology	4.120	1.668 – 10.174	**0.002**
Generalized convulsive SE	0.439	0.157 – 1.230	0.12
NCSE in coma	1.058	0.258 – 4.336	0.94
Continuous intravenous anesthetic drugs	1.210	0.399 – 3.671	0.74
Refractoriness to 1st- and 2nd-line medication	2.778	0.884 – 8.734	0.080
Good outcome in survivors to discharge			
New AEDs	2.642	1.164 – 5.995	**0.02**
Age ≥ 65 years	0.222	0.088 – 0.558	**0.001**
History of seizures	2.420	1.087 – 5.389	**0.03**
Potentially fatal etiology	0.194	0.081 – 0.464	< **0.001**
Generalized convulsive SE	2.343	1.033 – 5.314	**0.04**
NCSE in coma	0.673	0.116 – 3.912	0.66
Continuous intravenous anesthetic drugs	0.448	0.154 – 1.305	0.14
Refractoriness to 1st-and 2nd-line medication	0.157	0.059 – 0.414	< **0.001**
Premorbid mRS	1.198	0.925 – 1.551	0.17

Variables showing a significant association with the outcome of interest upon univariate comparison were included in binary logistic regression model with forced entry of the variable 'New AEDs'. Statistically significant values ($p < 0.05$) are expressed in bold. Abbreviations: SE status epilepticus, NCSE nonconvulsive status epilepticus, AED antiepileptic drug.

dosing of first- and second-line medications, and the limited sample size precluding full adjustment for the heterogeneity of SE etiologies and SE courses. The main aspects of our findings are discussed below:

First, our observation that new AEDs were associated with higher odds for occurrence of RSE compares well with previous research [12,14]. In search for possible explanations for this association it appears noteworthy that we, like others, found that new AEDs were prescribed more often in simple and complex partial than in generalized convulsive SE [14]. This gives rise to the question whether variability in seizure semiology might link the prescription of new AEDs to RSE development. The results of a study on early predictors of RSE development, however, did not find such an association [25]. Furthermore, given that refractoriness to antiepileptic therapy is known to increase with growing seizure duration and that convulsive SE is less likely to be missed by emergency medical services [26], probably resulting in more timely initiation of treatment [27], one could even hypothesize a lower risk of RSE development in convulsive SE as compared to SE with a less obvious seizure semiology.

Second, we did not find the higher odds of RSE occurrence observed among patients treated with new AEDs to translate into higher in-hospital mortality rates. This finding can possibly be explained by the fact that the etiology underlying an SE episode is the overwhelming predictor of death in SE patients and that there were similar proportions of patients with a potentially fatal SE etiology in both the new and traditional AED cohorts of our study population [2,28,29]. Thus, the higher odds of RSE development associated with the choice of newer AEDs for second-line treatment may not substantially contribute to the risk of death during hospital stay, even though RSE development itself worsens SE prognosis [9].

Third, application of new AEDs was independently associated with both RSE development but also of favorable short-term outcome according to the definition applied in this study. This finding appears contradictory, but one can find hypothetical explanations for it, including the very definition of RSE as seizures unresponsiveness to application of two AEDs: New AEDs carry a favorable side effect profile and this allows them to be administered very rapidly. It is possible that this may lead emergency department physicians to escalate SE therapy to a third-line treatment before the second-line medication has had adequate time to act [12]. This could result in a higher rate of SE episodes categorized as RSE when patients receive new AEDs for second-line treatment, despite that their seizures might have been successfully terminated by the second-line agent already. Following this hypothesis, there may be a difference between RSE episodes depending on whether they are defined by failure of a new or by failure of a traditional AED, with seizure activity possibly being "truly refractory" rather when persisting after application of a traditional AED. Another explanation could be that functional outcome was better in patients treated with new AEDs because these carry a lower risk of potentially hazardous adverse effects. This would be in line with previous studies examining the use of new AEDs in conditions other than SE, e.g., in newly diagnosed epilepsy [30,31]. Additionally, overall treatment of patients in SE may have improved over the course of the study period, leading to better outcome after SE in general which, due to growing prescription rates over time, was found to be associated with newer AEDs in our study, although these may not be the main contributor to better outcome.

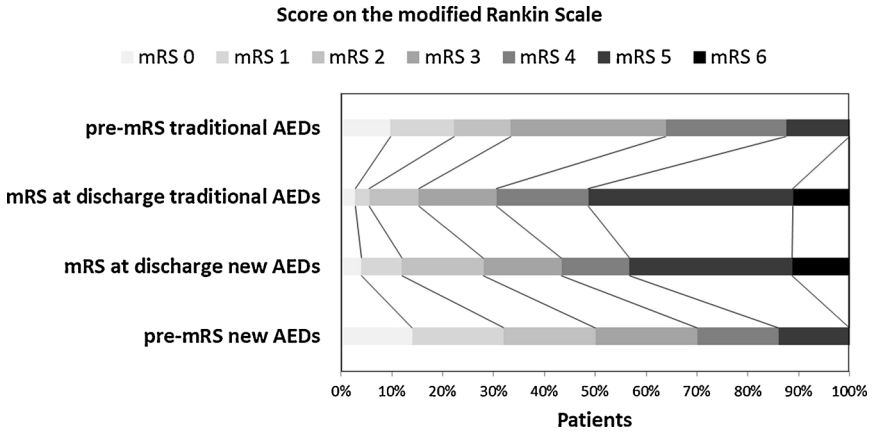

Fig. 4. Bar chart of functional outcome after traditional and new AEDs.
Abbreviations: AED antiepileptic drug, mRS modified Rankin Scale.

A strength of this study is the focus on the comparison of traditional vs new AEDs exclusively in episodes in which these were used as second-line treatment, which differs from previous research which assessed the effects of new AEDs applied at an undefined time at some point during an SE episode [12,14]. Our study thus mirrors the situation in emergency departments, where incoming SE patients often have already received pre-hospital first-line treatment with benzodiazepines.

The main limitations of this study were already briefly addressed in the introduction of this paragraph. In addition to the above mentioned inability to adjust our analyses for dosing and timing of first- and second-line medications, differences in choice of first-line benzodiazepines, which were shown to have potential impact on SE prognosis [28], could also not be considered in our calculations due to the limited sample size. Even though the compared cohorts appeared well balanced, as indicated by a non-significant difference in overall numbers of AEDs administered as well as similar proportions of patients with a potentially fatal etiology, a history of seizures, and continuous intravenous anesthetics for SE treatment, the heterogeneity of SE etiologies and courses may have not been adequately reflected by the limited number of variables available to characterize them [7,32]. Regarding second-line medications, there was a clear predominance of levetiracetam, valproic acid, and phenytoin. Other AEDs were only rarely applied, but for reasons of comparability with previous research, we chose to include those cases into the study and dichotomize the study population into treated with new vs traditional AEDs, although, in actuality, the comparison was mainly between levetiracetam vs valproic acid and phenytoin [12,14]. Our definition of good outcome, which also included patients with an mRS of > 2 as long as the mRS was not higher at time of hospital discharge compared to premorbid baseline, limits comparability with previous SE research using mRS cutoffs exclusively for outcome dichotomization.

5. Conclusion

In our study, we found an association of new AEDs with higher odds of RSE occurrence, however also with better functional outcome at discharge. The validity of these results is limited by methodological shortcomings inherent in our study design and thus needs to be confirmed in future research. In this regard, the results of the Established Status Epilepticus Treatment Trial (ESETT) will be of particular interest [13].

Authors' contributions

CR and DM: study concept and design, data acquisition, analysis and interpretation of data, statistical analysis, creation of figures, manuscript drafting. HBH: study concept and supervision, data interpretation, manuscript drafting. MIS, JAS, TMM, MH, STG, JBK, HMH: critical revision for important intellectual content.

All authors have read the manuscript, agreed with the contents, and approved the final version of the manuscript.

Ethical publication statement

The study was approved by the local ethics committee of the Friedrich- Alexander University Erlangen-Nürnberg (FAU), Germany (vote number: 48_15Bc). Given the retrospective nature of the study, the need for informed consent was waived. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

DM received unrestricted grants from UCB Pharma. HBH received unrestricted grants from UCB Pharma, Medtronic, Daiichi-Sankyo, and Novartis, furthermore personal fees from Boehringer Ingelheim and CSL Behring. HMH received grants from the EU and served on the scientific advisory boards of Cerbomed, Desitin, Eisai, Bial, and UCB Pharma. He received personal fees from IQWiG. He served on the speakers' bureau of or received unrestricted grants from Desitin, Eisai, Novartis, Bial, Hexal, Boehringer Ingelheim, and UCB Pharma. JBK reports grants from Covidien (Medtronic), personal fees from Bayer, Pfizer, and Sanofi. The remaining authors report no conflicts of interest.

Declaration of Competing Interest

DM received unrestricted grants from UCB Pharma. HBH received unrestricted grants from UCB Pharma, Medtronic, Daiichi-Sankyo, and Novartis, furthermore personal fees from Boehringer Ingelheim and CSL Behring. HMH received grants from the EU and served on the scientific advisory boards of Cerbomed, Desitin, Eisai, Bial, and UCB Pharma. He received personal fees from IQWiG. He served on the speakers' bureau of or received unrestricted grants from Desitin, Eisai, Novartis, Bial, Hexal, Boehringer Ingelheim, and UCB Pharma. JBK reports grants from Covidien (Medtronic), personal fees from Bayer, Pfizer, and Sanofi. The remaining authors report no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.seizure.2019.11.003.

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