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Factors predicting cessation of status epilepticus in clinical practice – data from a prospective observational registry (SENSE)

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Running title: Treatment of status epilepticus in clinical practice

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Abstract

Objective: To investigate the initial termination rate of status epilepticus (SE) in a large observational study, and to explore associated variables.

Methods: Data of adults treated for SE were collected prospectively in centers in Germany, Austria, and Switzerland, during 4.5 years. Incident episodes of 1,049 patients were analyzed using uni- and multivariate statistics to determine factors predicting cessation of SE within 1 hour (for generalized convulsive SE, GCSE) and 12 hours (for non-GCSE) of initiating treatment.

Results: Median age at SE onset was 70 years; most frequent etiologies were remote (32%) and acute (31%). GCSE was documented in 43%. Median latency between SE onset and first treatment was 30 minutes in GCSE and 150 minutes in non-GCSE. The first intravenous compound was a benzodiazepine in 86% in GCSE, and 73% in non-GCSE. Bolus doses of the first treatment step were lower than recommended by current guidelines in 76% of the GCSE patients and 78% of the non-GCSE patients. In 319 GCSE patients (70%), SE was ongoing 1 hour after initiating treatment, and in 342 non-GCSE patients (58%) 12 hours after initiating treatment. Multivariate Cox regression demonstrated that the use of benzodiazepines as first treatment step, and a higher cumulative dose of anticonvulsants within the first period of treatment were associated with shorter time to cessation of SE for both groups.

Interpretation: In clinical practice, treatment guidelines were not followed in a substantial proportion of patients. This under-dosing correlated with lack of cessation of SE. Our data suggest that sufficiently dosed benzodiazepines should be used as first treatment step.

Introduction

Evidence regarding status epilepticus (SE) treatment, one of the most frequent neurological emergencies associated with increased morbidity and mortality, is still scarce. There are only few large randomized controlled trials (RCTs) fulfilling criteria of Class-1 evidence, all focusing on the first treatment step.[1-4] All studies were restricted to generalized convulsive SE forms, and three of them[1-3] exclusively investigated the effect of pre-hospital treatment. Those studies reported treatment success as high as 84% following initial administration of pharmacological agents. Real world data, however, suggest that termination rates are lower in clinical practice.[5,6] With the exception of the Veterans Affairs Study[4] and the ongoing ESET-Trial (ClinicalTrials.gov Identifier: NCT01960075), both from the USA, prospective controlled trials of in-hospital treatment of established SE and outcome have not been conducted. Furthermore, data on how guidelines based on these prospective trials have been implemented in clinical practice are limited, especially for Europe.

Therefore, a working group of centers from German-speaking countries established a prospective registry for patients treated for SE, with the acronym SENSE (Sustained Effort Network for treatment of Status Epilepticus).[7,8] It includes data on all treatment stages reflecting clinical practice, which were evaluated to determine predictors of cessation of SE within the first hour (for GCSE) and initial 12 hours (for non-GCSE) of treatment.

Methods

The methods and design of the SENSE registry have been published elsewhere.[7,8] In brief, eight centers with special expertise in SE treatment in German-speaking countries participated and recruited patients: Germany: Epilepsy Centre University Marburg, University Hospital Schleswig-Holstein Campus Kiel, Klinikum Osnabrück, Krankenhaus Barmherzige Brüder Regensburg; Austria: Christian-Doppler-Klinik, Universitätsklinikum der Paracelsus Medizinischen Universität Salzburg, Department of Neurology, Innsbruck Medical University; Switzerland: University Hospital Basel, University Hospital Lausanne (the only French-speaking site). The study was approved by the appropriate local ethics committees and registered at the German Clinical Trials Register (DRKS00000725). The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines[9] were followed.

SE was operationally defined as seizure duration of five minutes or longer, or consecutive seizures without returning to baseline for more than five minutes, or in comatose patients who fulfilled the electroencephalogram (EEG) criteria for non-convulsive SE as defined by Beniczky et al.[10] Patients with status-like phenomena owing to hypoxic brain injury, and patients under the age of 16 years were excluded.

We prospectively documented the following variables: demographics, health-related parameters, including SE etiology and comorbidities unrelated to it, SE onset, SE semiology, treatment, and outcome. We used the modified Rankin scale (mRS)[11,12] for global assessment of health before SE onset and at hospital discharge, and the status epilepticus severity score (STESS).[13] Patients who experienced generalized convulsive semiology during

the course of SE were considered as generalized convulsive SE (GCSE) patients. All other patients were considered as non-GCSE patients.

In many guidelines, refractoriness of SE is defined as ongoing SE after administration of an adequate dose of a benzodiazepine followed by an adequate dose of a non-benzodiazepine anticonvulsant drug. In clinical practice, SE treatment frequently does not follow guidelines, but consists of the administration of multiple relatively low doses of one or more benzodiazepines and non-benzodiazepine intravenous anticonvulsants.[5,14] Frequently, two or more agents are administered at the same time, or after a very brief interval. If a second compound is used before the previous one has had adequate time to penetrate the blood-brain barrier, efficacy of the first compound will be underestimated. Thus, treatment success cannot easily relate to individual treatment steps in clinical practice.

To assess the factors contributing to the success of the first phase of treatment, we defined 'first steps treatment success' for GCSE patients as cessation of SE within the first hour after treatment initiation. For non-GCSE patients, we chose a prolonged time frame of 12 hours instead: this should account for the fact that in several instances of non-convulsive or focal motor SE a less aggressive approach of treatment may be appropriate.[15,16] In addition, in non-motor SE, determining treatment success at night is not possible because continuous EEG monitoring is not routinely available in many European centers, or is restricted to patients with super-refractory SE.

Statistical analysis was performed with IBM SPSS Version 25 (Chicago, Illinois, USA). For univariate analysis of categorical data, chi-square test and Fisher's exact test were used.

Interval scaled, or ordinal scaled data were analyzed using Mann–Whitney U test (comparison of two groups), or Kruskal–Wallis test (comparison of three or more groups).

To determine the contribution of individual factors to the success of the first treatment step, we used multivariate, stepwise (backward) Cox regression (p=0.05 for inclusion and exclusion). Time to SE cessation was chosen as dependent variable, with censoring of the time at one hour (GCSE patients), respectively 12 hours (non-GCSE patients) after first treatment. Patients who died within the first hour (GCSE patients), respectively 12 hours (non-GCSE patients) of treatment time, were considered as ongoing SE for this analysis. The following variables were considered for the multivariate analysis: age, gender, presence of acute etiology, mRS before onset, STESS, latency to first treatment, use of benzodiazepines as first step, and cumulative standardized dose of anticonvulsant agents (including benzodiazepines) per kg bodyweight used within the first 30 minutes (GCSE patients), respectively 60 minutes (non-GCSE patients). For standardization, we divided the bolus dose actually administered by the bolus dose recommended by the treatment guidelines of the German, Austrian and Swiss scientific societies[16] for SE in adults and multiplied the result by 100. If the guidelines recommended a bolus dose range, the mean of upper and lower limit was considered as recommended for calculation purposes. Only patients for whom latencies and bolus doses could be determined with sufficient validity and precision were included in the multivariate analysis.

Results

Between January 2011 and June 2015, 1,049 patients with 1,179 episodes of SE were enrolled in SENSE. For our analysis, only the first episode of each patient was included. The clinical characteristics (i.e., demographics, etiology, semiology, comorbidities) are shown in tables 1 and 2.

Median age at SE onset was 70 years (interquartile range [IQR], 54–80 years), and 51% of the patients were women. Most frequent etiologies were remote symptomatic, closely followed by acute symptomatic factors, or a combination of both. Almost half of the patients had generalized tonic-clonic seizure symptoms during the SE. Less than half of the patients had no impairment of their everyday life by signs or symptoms of a pre-existing health disorder, as signified by a mRS of 0–2.

SE treatment was initiated within 30 minutes in 221 of 457 GCSE patients (48%), and in 112 of 592 non-GCSE patients (19%). Median latency between SE onset and treatment was 30 minutes (IQR, 25–240) for the GCSE patients, and 150 minutes (IQR, 45-420) for the non-GCSE patients. The first treatment step, most frequently one or a combination of several benzodiazepines, was successful in 98 GCSE patients (21%), and 93 non-GCSE patients (16%), details are included in tables 3 and 4. In patients with GCSE, levetiracetam (LEV) was used as first treatment step only in 28 cases (6%), whereas in non-GCSE, 130 patients (22%) received LEV as first treatment step. The second treatment step was administered in 359 GCSE patients and in 499 non-GCSE patients after a median latency of 30 minutes from start of administration of the first drug, and was successful in 46% of the GCSE patients, and in 38% of the non-GCSE patients (thus, the total success rate of the first two steps was 58% for the

GCSE patients, and 47% for the non-GCSE patients) (supplemental table 1). LEV was most frequently used (227 GCSE patients and 307 non-GCSE patients), followed by valproate (40 GCSE patients and 71 non-GCSE patients).

Treatment lasted between a few minutes and more than 55 days (median, 272 minutes; IQR, 55–2,457 minutes). Bolus doses of intravenous compounds were considerably lower than recommended in current treatment guidelines (supplemental table 2). Bolus doses of lorazepam were significantly lower than recommended both in refractory GCSE ($p<0.05$) and refractory non-GCSE ($p<0.01$) patients. The other individual agents did not differ significantly between groups. However, cumulative standardized bolus doses applied in the first 0.5, 2, and 12 hours of treatment, respectively, were significantly lower in refractory compared to non-refractory GCSE patients, as well as in refractory non-GCSE patients compared to non-refractory non-GCSE patients ($p<0.001$). A significantly ($p<0.001$) higher proportion of non-GCSE patients with ongoing SE was intubated during treatment.

In 439 GCSE patients (96%) and 540 non-GCSE patients (91%), SE ceased during the in-hospital stay: within the first 0.5 hours after treatment initiation in 97 GCSE patients (24%), and 73 non-GCSE patients (15%); after 2 hours in an additional 91 GCSE patients (20%) and 78 non-GCSE patients (13%); and after 12 hours in an additional 98 GCSE patients (21%) and 98 non-GCSE patients (17%). In-hospital mortality was 9% (43 patients) for GCSE and 19% (114 patients) for non-GCSE (see table 5). Both refractory GCSE patients and non-GCSE patients had a higher chance of worsening in mRS at discharge compared to non-refractory patients.

Compared to GCSE patients with ongoing SE after 1 hour of treatment, those GCSE patients treated successfully were younger ($p<0.01$), and they had a shorter treatment latency ($p<0.001$), a higher rate of benzodiazepines as first treatment step ($p<0.001$), a shorter interval between the first two treatment steps ($p<0.001$), and a higher standardized cumulative dose of anticonvulsants within the first 30 minutes of treatment ($p<0.001$). In non-GCSE patients, subjects treated successfully within the first 12 hours were younger ($p<0.001$), had lower STESS, received more often benzodiazepines as first step treatment ($p<0.001$), had a shorter interval between the first two treatment steps ($p<0.001$), and a higher standardized cumulative dose of anticonvulsants ($p<0.001$); treatment latency failed to reach significance (p=0.059). There was no significant difference regarding etiology between refractory and non-refractory patients in both SE subgroups.

Multivariate analysis (supplemental table 3) showed that in GCSE patients, younger age (hazard ratio (HR) 0.89 – 95% confidence interval (CI) 0.82-0.97, p=0.01), lower mRS before SE onset (HR 0.89 – 95%CI 0.8-0.99, p=0.05), the application of a benzodiazepine as initial drug (HR 9.62 – 95%CI 1.34-69.3, p=0.04), a higher cumulative dose of anticonvulsant agents given within the first 30 minutes of treatment (HR 1.02 - 95%CI1.01-1.03, p=0.002), and shorter latency from SE onset to treatment initiation (HR 0.89 – 95%CI 0.82-0.97, p=0.04) independently predicted a shorter time to cessation of SE within the first hour of treatment. In non-GCSE patients, significant factors associated with a shorter time to SE cessation within the first 12 hours were lower STESS (HR 0.8 95%CI 0.73-0.88, $p<0.001$), lower number of comorbidities (HR 0.89 – 95%CI 0.81-0.97, p=0.004), use of a benzodiazepine as first drug

(HR 1.96 – 95%CI 1.36-2.84, p<0.001), and higher cumulative standardized drug dose within the first 60 minutes (HR 1.01 – 95%CI 1.01-1.02, p=0.002).

Discussion

This study relies on a large prospective observational adult SE registry, reflecting situations occurring in clinical practice in several European hospitals. It shows that in the vast majority of patients, SE ceases during the hospital stay. However, the success rate of the first treatment steps – regardless of the compound used – was much lower than reported in randomized controlled studies. In addition, bolus doses in most cases tended to be lower than recommended by guidelines. Moreover, in 15% of patients, benzodiazepines were not used as first-line agents. The use of benzodiazepines as first treatment step, and the cumulative dose of all agents applied within the first 30-60 minutes of treatment had significant influence on SE cessation within the first hours of treatment, independently from other outcome predictors. This holds true both for patients with GCSE and with non-GCSE.

SE ceased within the first 30 minutes in only 16% and in 51% of patients within 12 hours following treatment initiation. Globally, this appears to be much lower than reported in randomized trials, where treatment responses within the first hour ranged between 76–81%[17], 44–65%[4], 43–59%[1], 63–73%[3], and 74–84%[2]. Interestingly, the only randomized study that included a placebo arm reported a success rate of 16%,[1] which is similar to our findings. However, these studies essentially focused on generalized convulsive SE with a

fixed treatment protocol, allowing observation of the benzodiazepine effect before administering a subsequent compound.

This differs from common clinical practice outside an RCT setting, where intravenous antiepileptic drugs (AEDs) are often given virtually at the same time of the first treatment step.[5,6,18,19] For example, in a recent multicenter observational study in European and US centers, 156/177 (88%) adult patients received a second anticonvulsant after a benzodiazepine, and the latter was underdosed in 59% of cases, as compared with existing guidelines.[5] In addition, our cohort included, on average, considerably older patients, with a higher rate of severe comorbidities compared with the randomized trials. Furthermore, in the present study, as in other observational population-based[20,21] or hospital cohorts,[5,6] only a proportion of around 50% had generalized convulsive SE, as opposed to RCTs specifically recruiting patients with this SE type. Concluding that benzodiazepines were efficacious in only 12% of cases (which is even lower than placebo in the study by Alldredge and colleagues[1]) would therefore be misleading.

In contrast with the low success rate of the first treatment step, more than 90% of SE ceased during in-hospital stay. At first glance, it seems surprising that SE was eventually controlled in almost all patients despite the initial delays and underdosing of anticonvulsants. Several considerations are important: firstly, SE control does not necessarily result in a favorable outcome in terms of mRS or quality of life in these patients – ongoing SE may result in survival with new impairments; secondly, patients in the study were not left without

treatment, but received many different anticonvulsants, which may have needed time to reach maximum efficacy.

Ultimately, there may have been good clinical reasons to avoid strict adherence to guidelines for the treatment of generalized convulsive SE. This is most likely in multi-morbid, frail, and elderly patients with non-convulsive SE, in whom therapeutic coma using intravenous anesthetics is frequently avoided, due to the risks of artificial ventilation and cardiovascular depression inherent to this therapy, which is associated with increased mortality, infection rate,[22-24 22-24] and length of hospital stay.[22-24]

Benzodiazepines were used as a first-line agent in 81% of the events, while LEV (15%) or other non-benzodiazepine anticonvulsants were used as alternatives. This is consistent with several observational and registry studies showing that the majority of patients do receive benzodiazepines as first-line (90%;[25] 93%;[26] 97%[6]). A Swiss study found a rate of 16% deviation from the recommended sequence 'benzodiazepine -> intravenous non-benzodiazepine anticonvulsant', which is comparable with our results.[14] A recent study of emergency treatment of out-of-hospital SE[27] showed that early treatment with a benzodiazepine depended on the SE semiology. Patients with non-convulsive SE were at risk of not receiving early benzodiazepine treatment in comparison with those with convulsive SE. Thus, a correlation between prominence of motor symptoms and subsequent SE treatment could partly explain our results.

Our findings strongly suggest that the initial administration of a benzodiazepine *versus* a non-benzodiazepine intravenous anticonvulsant predicts earlier SE cessation. This supports

current treatment guidelines[16,28,29] and the results from the pivotal trials that these guidelines are based on.[1,3,4] For example, the 'Veterans Affairs trial'[4] provided evidence that lorazepam (0.1 mg/kg, 64.9%) was significantly ($p<0.001$) more effective in controlling overt convulsive SE than phenytoin (18 mg/kg, 43.6%).

There is evidence that benzodiazepines are more effective than placebo,[1] that lorazepam is better than diazepam,[30] and that intramuscular midazolam is superior to intravenous lorazepam when administered rapidly en route to the hospital before establishing an intravenous access.[3] Results regarding the relative efficacy of LEV, the non-benzodiazepine intravenous anticonvulsant drug most frequently used as first-line treatment instead of a benzodiazepine in our registry, are variable. The simultaneous application of 2.5 g LEV with 1 mg clonazepam had no additional effect on the cessation rate of generalized convulsive SE after 10 minutes compared with clonazepam alone,[2] and a retrospective study suggested that LEV was less effective than valproic acid as second-line therapy.[31] Our findings suggest that LEV may be less efficacious than benzodiazepines as first-line drug.

A higher cumulative weight-adjusted dose of anticonvulsants was associated with a higher likelihood of SE cessation within the first hour in GCSE patients, and within the first 12 hours in non-GCSE patients, in a dose-related manner, indicating that underdosing is a risk factor for non-cessation of SE. There is evidence from RCTs that the application of a second dose of anticonvulsants is effective in the majority of patients who continue to seize after the first-line dose.[1,3,17] Accordingly, guidelines recommend administering an additional dose of benzodiazepine or other anticonvulsant if SE is not initially controlled.[15,16,29] This

recommendation is also supported by our data. On the other hand, overtreatment may put patients at risk for harmful adverse events, since it is associated with a higher need for intubation and a longer duration of hospitalization.[32] This risk needs to be weighted against the risks of ongoing SE, associated with a higher proportion of worsening in mRS in refractory patients in our cohort.

Our data do not suggest superiority or inferiority of one particular substance compared to others. Analysis of the relative value of different benzodiazepines shows no significant difference between lorazepam, midazolam, diazepam or a combination when used as first substance (figure 1). In addition, overall success rates of non-benzodiazepine substances used in 50 or more patients were all between 38% and 44%[8].

One could assume that a higher cumulative dose of benzodiazepines, non-benzodiazepine anticonvulsants, or both in the early phase of treatment carries a higher risk of significant sedation and respiratory insufficiency as side-effect. However, this putative effect did not result in a higher proportion of intubation for airway protection in both GCSE and non-GCSE patients with SE cessation within one hour (resp. 12 hours) despite a significantly higher cumulative dose of both benzodiazepines and other anticonvulsants. Moreover, only a very small minority of patients with SE cessation within the first 12 hours were aggressively treated with intentional anesthesia for SE treatment. Our findings are supported by data from a large placebo-controlled study of ambulance-based treatment of convulsive SE [1]that showed that the risk of respiratory insufficiency in the placebo arm was much higher than in the treatment arms (lorazepam and diazepam).

Latency from SE onset to treatment showed significant contribution to the risk of ongoing SE in GCSE patients. In non-GCSE patients, significance was missed in univariate analysis (p=0.06) and in multivariate analysis (p=0.28). Patients who received first treatment very early were very likely to receive benzodiazepine treatment as first step and possibly in a higher dose. Therefore, the contribution of early treatment could have been masked. Age was a significant predictor of refractoriness in multivariate analysis only for GCSE patients. For non-GCSE patients, significance was missed. This could be explained by the generally older age of the non-GCSE patients and thus the smaller interquartile range that may have masked the effect. The same effect may apply for the mRs before SE onset which also reached significance only for the GCSE group.

The number of comorbidities was a significant predictor of time to SE cessation only in the non-GCSE group. In this group, the median duration of in-patient treatment was higher. In our protocol, treatment-associated complications or hospital-associated disorders such as pneumonia or other infections were documented as comorbidities. Therefore, the larger difference of duration of treatment between the refractory and the non-refractory non-GCSE patients may be the underlying confounder for reaching significance.

STESS was a significant predictor of non-cessation of SE only for the non-GCSE group. This group contains patients with non-convulsive SE (NCSE) in coma as well as patients with focal motor SE or dyscognitive SE. Patients with NCSE in coma score 2 points in the STESS category 'worst seizure type', and are more likely to be refractory[33], whereas non-GCSE patients without coma score 0 points for 'worst seizure type' in STESS. In contrast to that, all GCSE

patients score 1 point in this STESS category, resulting in a smaller interquartile range. Therefore, STESS - which was developed to predict mortality and not refractoriness[13] - seems to be able to predict refractoriness only in the more heterogenous group of non-GCSE patients.

Non-GCSE patients treated in German centers had a higher risk of refractoriness in univariate analysis. In German centers, patients tended to be older. Older age is associated with infavorable outcome[34]. In addition, in German centers lorazepam was used much more frequently. A retrospective analysis of SE data from four centers[5] could demonstrate that the use of lorazepam was associated with an increased risk of refractoriness, most likely as a consequence of underdosing.

This study has several limitations. Firstly, contributions of different centers in terms of patient numbers were fairly divergent, decreasing the cohort homogeneity, and potentially impacting generalizability. In addition, there was no independent comparison between hospital coding of SE data and database entry. It is possible that this led to reporting bias, especially under-ascertainment. In addition, treatment was neither randomized nor controlled. Therefore, correlations between treatment data and outcome must be interpreted with caution. Moreover, cases excluded from multivariate analysis were not randomly distributed (see supplementary table 1). Thus, the results may have been biased by cases with missing information. Continuous EEG (cEEG) was not available for most of the

patients. It should be stressed that this is suboptimal care. Academic societies and patient organisations should press for separate reimbursement of cEEG in SE patients. This would allow European hospitals to establish the standards of care already available in most U.S. centers.

On the other hand, our database documents 'real life' treatment in clinical practice, in centers with special interest in SE treatment, and the previously published, standardized ascertainment protocol should limit marked internal bias.[7] The number of patients included was clearly higher than in comparable registries or trials. The sample size and heterogeneity, based on cohorts from three countries, from both university hospitals and non-academic hospitals, allow thorough statistical analysis, and support generalizability.

Current guidelines on the treatment of SE are based on studies almost exclusively investigating patients with generalized convulsive SE, or on small and uncontrolled studies. We hope that our findings will help improve adherence to current treatment guidelines on the use of benzodiazepines and the use of sufficiently high doses in the first steps of therapy, and thereby improve the quality of patient care. Moreover, the registry may prove an important tool for generating hypotheses regarding treatment and outcome of SE, and may help design conclusive therapy trials.

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Author contributions

CK, AOR, FR, IU, NL, CT, ET and SR developed the study concept and design. CK, AOR, FR, IU, NL, CT, SR, RS, AS, ET and ZU were responsible for the data collection. All authors were responsible for data analysis. CK drafted the first version of the manuscript.

Potential Conflicts of Interests

This manuscript mentions several anticonvulsant drugs, and the relationships of authors with the pharmacological companies producing these or other anticonvulsant drugs are noted below:

CK received speaker honoraria from UCB Pharma (levetiracetam, lacosamide, brivaracetam) and Eisai (zonisamide, eslicarbazepine, perampanel, rufinamide). He served on advisory boards for Eisai and UCB Pharma.

ET has acted as a paid consultant to Eisai, Bial (eslicarbazepine acetate), GW Pharma (cannabidiol), and UCB Pharma and has received speaker honoraria from Bial, Eisai, GW Pharma, Newbridge (lacosamide), Viropharma (midazolam), and UCB Pharma in the past three years. He has received research funding from UCB Pharma and Eisai.

FR received personal fees from Eisai, UCB Pharma, Desitin (diazepam, clonazepam, levetiracetam, valproate, phenytoin, phenobarbital, oxcarbazepine, carbamazepine), Hexal (valproate, levetiracetam, midazolam), Novartis (oxcarbazepine), GW-Pharma, Shire (midazolam), as well as research grants from UCB Pharma.

IU received speaker honoraria from UCB Pharma and Eisai. She served on advisory boards for UCB Pharma and Eisai.

NL received a research grant from UCB Pharma, travel grants from UCB Pharma and Eisai, speaker honoraria from UCB Pharma, Eisai, Desitin and Janssen-Cilag (topiramate) and has served as a paid consultant for UCB Pharma and Eisai.

SR received unconditional research grants from UCB, honoraria from serving on the scientific advisory boards of Desitin, Eisai, and UCB, travel grants from Janssen-Cilag, and UCB, speaker fees from UCB, and from serving as a consultant for Eisai, Janssen-Cilag, and UCB.

AS reports personal fees and grants from Desitin, Eisai, and UCB Pharma.

CT received honoraria from Eisai, Desitin and UCB Pharma. He served on the scientific advisory boards of Eisai.

TWM received financial support from Desitin for visiting scientific meetings and received honoraria for speaking engagements from Eisai and Desitin.

AOR and ZU have nothing to disclose.

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Figure Legend

Kaplan-Meier analysis of cumulative patients with ongoing status epilepticus (SE). Time from treatment initiation was censored at 1 hour for patients with generalized convulsive SE (GCSE) (a) and at 12 hours for patients with non-GCSE (b). Patients who died within the period were considered as ongoing SE for this analysis.

CLZP, clonazepam; comb, combination of two or more benzodiazepines as first treatment step; DZP, diazepam; LEV, levetiracetam; LZP, lorazepam; MDZ, midazolam.

Table 1: Characteristics of patients with GCSE

		All patients with GCSE (n=457)	**GCSE – cessation within 60 minutes (n=138)**	**GCSE – non-cessation within 60 minutes (n=319)**
Country	Germany	**199**	57 (29%)	142 (71%)
	Austria	**98**	32 (33%)	66 (67%)
	Switzerland	**160**	49 (31%)	111 (69%)
Age (years)	Median (range)	**65 (18-100)**	58 (19-97)	67 (18-100)**
	IQR	**49-78**	41-75	54-79
Gender	Female	**203**	53 (26%)	150 (74%)
	Male	**254**	85 (34%)	169 (66%)
mRS before onset	0-2	**185**	70 (38%)	115 (62%) *
	3	**112**	33 (30%)	79 (70%)
	4	**95**	21 (22%)	74 (78%)
	5	**65**	14 (22%)	51 (79%)
Comorbidities (number)	Median (IQR)	**2 (1-3)**	2 (1-3)	2 (1-3)
Pre-existing epilepsy	yes	**227**	77 (34%)	150 (66%)
Etiology	Acute symptomatic only	**151**	42 (28%)	109 (72%)
	Acute on remote	**52**	16 (31%)	36 (69%)
	Remote symptomatic only	**141**	56 (40%)	85 (60%)
	Progressive	**57**	16 (28%)	41 (72%)
	Unknown/other	**56**	8 (14%)	48 (86%)
STESS	Median (IQR)	**3 (3-4)**	3 (2-4)	3 (2-4)
	STESS ≤2	**128**	39 (31%)	89 (69%)

SE, status epilepticus; GCSE, generalized convulsive SE; IQR, interquartile range (25^{th}-75^{th} quartile); mRS, modified Rankin Scale; STESS, SE severity score;

*p<0.05; **p<0.01; ***p<0.001 for comparison between cessation group and non-cessation group

Table 2: Characteristics of patients with non-GCSE

		All patients with non-GCSE (n=592)	Non-GCSE – cessation within 12 hours (n=250)	Non-GCSE – non-cessation within 12 hours (n=342)
Country	Germany	**278**	80 (29%)	198 (71%) ***
	Austria	**116**	70 (60%)	46 (40%)
	Switzerland	**198**	100 (51%)	98 (49%)
Age (years)	Median (range)	**72 (18-100)**	68.5 (20-100)	74 (18-94)***
	IQR	**59-81**	55-79	64-83
Gender	Female	**334**	133 (40%)	201 (60%)
	Male	**258**	117 (45%)	141 (55%)
mRS before onset	0-2	**267**	125 (47%)	142 (53%)
	3	**144**	56 (39%)	88 (61%)
	4	**118**	48 (41%)	70 (59%)
	5	**63**	21 (33%)	42 (67%)
Comorbidities (number)	Median (IQR)	**3 (2-4)**	2 (1-4)	3 (2-4)**
Pre-existing epilepsy	yes	**258**	112 (43%)	146 (57%)
Etiology	Acute symptomatic only	**179**	82 (45%)	97 (55%)
	Acute on remote	**48**	16 (33%)	32 (67%)
	Remote symptomatic only	**193**	77 (40%)	116 (60%)
	Progressive	**106**	48 (45%)	58 (55%)
	Unknown/other	**66**	27 (41%)	39 (60%
STESS	Median (IQR)	**2 (2-3)**	2 (1-3)	2 (2-4)***
	STESS ≤2	**325**	159 (49%)	166 (51%)***

SE, status epilepticus; GCSE, generalized convulsive SE; IQR, interquartile range (25^{th}-75^{th} quartile); mRS, modified Rankin Scale; STESS, SE severity score;

*p<0.05; **p<0.01; ***p<0.001 for comparison between cessation group and non-cessation group

Table 3: First treatment step in patients with GCSE

		All patients with GCSE (n=457)	**GCSE – cessation within 60 minutes (n=138)**	**GCSE – non-cessation within 60 minutes (n=319)**
Latency from SE onset to first treatment step (min)	Median (range; IQR)	**30 (5-4970; 20-90) (425 valid cases)**	25 (5-1220; 15-60) (136 valid cases)	20 (5-4970; 20-120)*** (288 valid cases)
	≤ 30 min	**221**	86 (39%)	135 (61%)
	31-120 min	**121**	35 (29%)	86 (71%)
	2 h – 6 h	**48**	11 (23%)	37 (77%)
	6 h – 24 h	**57**	6 (11%)	51 (89%)
	>24 h	**10**	0	10
First step	LZP	**120**	35 (29%)	85 (71%)
	DZP	**24**	11 (46%)	13 (54%)
	CLZ	**87**	26 (30%)	61 (70%)
	MDZ	**59**	23 (39%)	36 (61%)
	Combined BZD	**122**	39 (32%)	83 (68%)
	LEV	**28**	1 (4%)	27 (96%)
	Other	**17**	3 (18%)	14 (82%)
BZD as first line therapy	Yes	**412**	134 (33%)	278 (67%) ***
First agent underdosed	Yes	**348**	107 (31%)	241 (69%)
First step successful	Yes	**98 (21%)**		

SE, status epilepticus; GCSE, generalized convulsive SE; BZD, benzodiazepines; CLZ, clonazepam; DZP=diazepam; h, hours; IQR, interquartile range (25th–75th quartile); LEV, levetiracetam; LZP, lorazepam; MDZ=midazolam; min, minutes;.Underdosed: bolus dose <70% of recommended bolus dose. Valid patients: patients where the documentation of application time resp. bolus dose was precisely documented.

***p<0.001 for comparison between cessation group and non-cessation group

Table 4: First treatment step in patients with non-GCSE

		All patients with non-GCSE (n=592)	**Non-GCSE – cessation within 12 hours (n=250)**	**Non-GCSE – non-cessation within 12 hours (n=342)**
Latency from SE onset to first treatment step (min)	Median (range; IQR)	**150 (5-13200; 45-420) (486 valid cases)**	120 (5-10425; 30-427) (246 valid cases)	180 (5-13200; 60-420) (240 valid cases)
	≤ 30 min	**112**	66 (59%)	46 (41%) ***
	31-120 min	**117**	58 (49%)	59 (51%)
	2 h – 6 h	**123**	57 (46%)	66 (54%)
	6 h – 24 h	**162**	41 (25%)	121 (75%)
	>24 h	**78**	28 (36%)	50 (64%)
First step	LZP	**198**	97 (49%)	101 (51%)
	DZP	**20**	9 (45%)	11 (55%)
	CLZ	**124**	64 (52%)	60 (58%)
	MDZ	**26**	11 (42%)	15 (58%)
	Combined BZD	**66**	32 (49%)	32 (51%)
	LEV	**130**	33 (25%)	97 (75%)
	Other	**28**	4 (14%)	24 (86%)
BZD as first line therapy	Yes	**437**	214 (49%)	223 (51%) ***
First agent underdosed	Yes	**467**	206 (44%)	261 (56%)
First step successful	Yes	**93 (16%)**		

SE, status epilepticus; GCSE, generalized convulsive SE; BZD, benzodiazepines; CLZ, clonazepam; DZP=diazepam; h, hours; IQR, interquartile range (25th–75th quartile); LEV, levetiracetam; LZP, lorazepam; MDZ=midazolam; min, minutes;.Underdosed: bolus dose <70% of recommended bolus dose. Valid patients: patients where the documentation of application time resp. bolus dose was precisely documented.

***p<0.001 for comparison between cessation group and non-cessation group

Table 5: Outcome data for patients with GCSE

		All patients with GCSE (n=457)	GCSE – cessation within 60 minutes (n=138)	GCSE – non-cessation within 60 minutes (n=319)
Intubation	Yes	**108**	30 (28%)	78 (72%)
For airway protection	Yes	**74**	24 (32%)	50 (68%)
For SE treatment	Yes	**34**	6 (18%)	28 (82%)
SE stopped during hospital stay	Yes	**439**	138 (31%)	301 (69%)
Treatment duration (min)	Median (IQR)	**150 (40-1265)**	20 (10-40)	540 (153-2767)***
Latency from last treatment to SE end (min)	Median (IQR)	**40 (10-460)**	10 (5-20)	225 (30-1095)***
mRS at discharge	0-2	**123**	59 (48%)	64 (52%)
	3	**111**	38 (34%)	73 (66%)
	4	**89**	21 (24%)	68 (76%)
	5	**92**	18 (20%)	74 (80%)
	6 (death during hospital stay)	**43**	3 (7%)	40 (93%) ***
Patients with no change of mRS		**317**	118 (37%)	199 (63%) ***
Duration of hospital stay (days)	Median (IQR)	**8 (4-16)**	5 (2-9)	10 (5-18)***

SE, status epilepticus; GCSE, generalized convulsive SE; NCSE, non-convulsive SE; IQR, interquartile range (25th–75th quartile); min, minutes; mRS= modified Rankin Scale;

***p<0.001 for comparison between cessation group and non-cessation group

Table 6: Outcome data for patients with non-GCSE

		All patients with non-GCSE (n=592)	Non-GCSE – cessation within 12 hours (n=250)	Non-GCSE – non-cessation within 12 hours (n=342)
Intubation	Yes	**89**	14 (16%)	75 (84%) ***
For airway protection	Yes	**37**	7 (19%)	30 (81%) **
For SE treatment	Yes	**52**	7 (13%)	45 (87%)
SE stopped during hospital stay	Yes	**540**	250 (46%)	290 (54%)
Treatment duration (min)	Median (IQR)	**500 (60-3440)**	30 (10-120)	1425 (850-3720)***
Latency from last treatment to SE end (min)	Median (IQR)	**180 (29-1200)**	75 (29-202)	3780 (1460-7512)***
mRS at discharge	0-2	**144**	91 (63%)	53 (37%)
	3	**95**	53 (56%)	42 (44%)
	4	**142**	59 (42%)	83 (58%)
	5	**97**	29 (30%)	68 (70%)
	6 (death during hospital stay)	**114**	18 (16%)	96 (84%) ***
Patients with no change of mRS		**305**	177 (58%)	128 (42%) ***
Duration of hospital stay (days)	Median (IQR)	**11 (5-20)**	7 (3-14)	14 (8-24)***

SE, status epilepticus; GCSE, generalized convulsive SE; NCSE, non-convulsive SE; IQR, interquartile range (25th–75th quartile); min, minutes; mRS= modified Rankin Scale;

** p<0.01; ***p<0.001 for comparison between cessation group and non-cessation group

Figure 1a: patients in GCSE after treatment onset

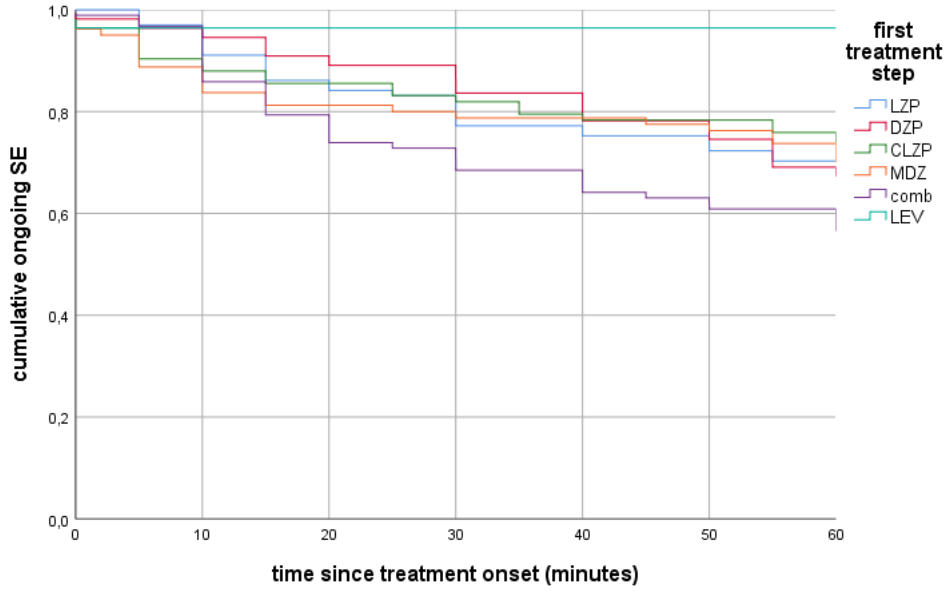

Figure 1b: patients in non-GCSE after treatment onset

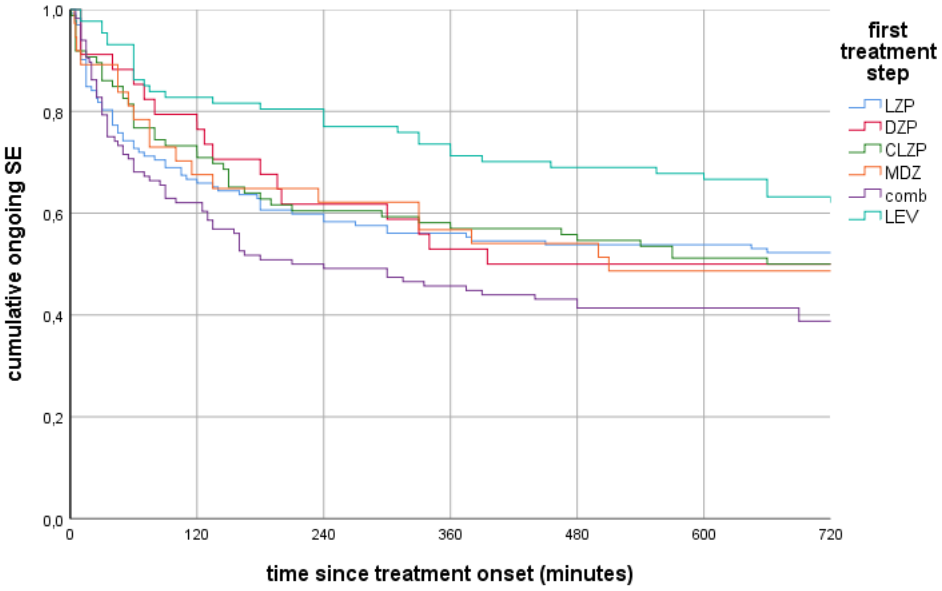

Figure 1a: patients in GCSE after treatment onset

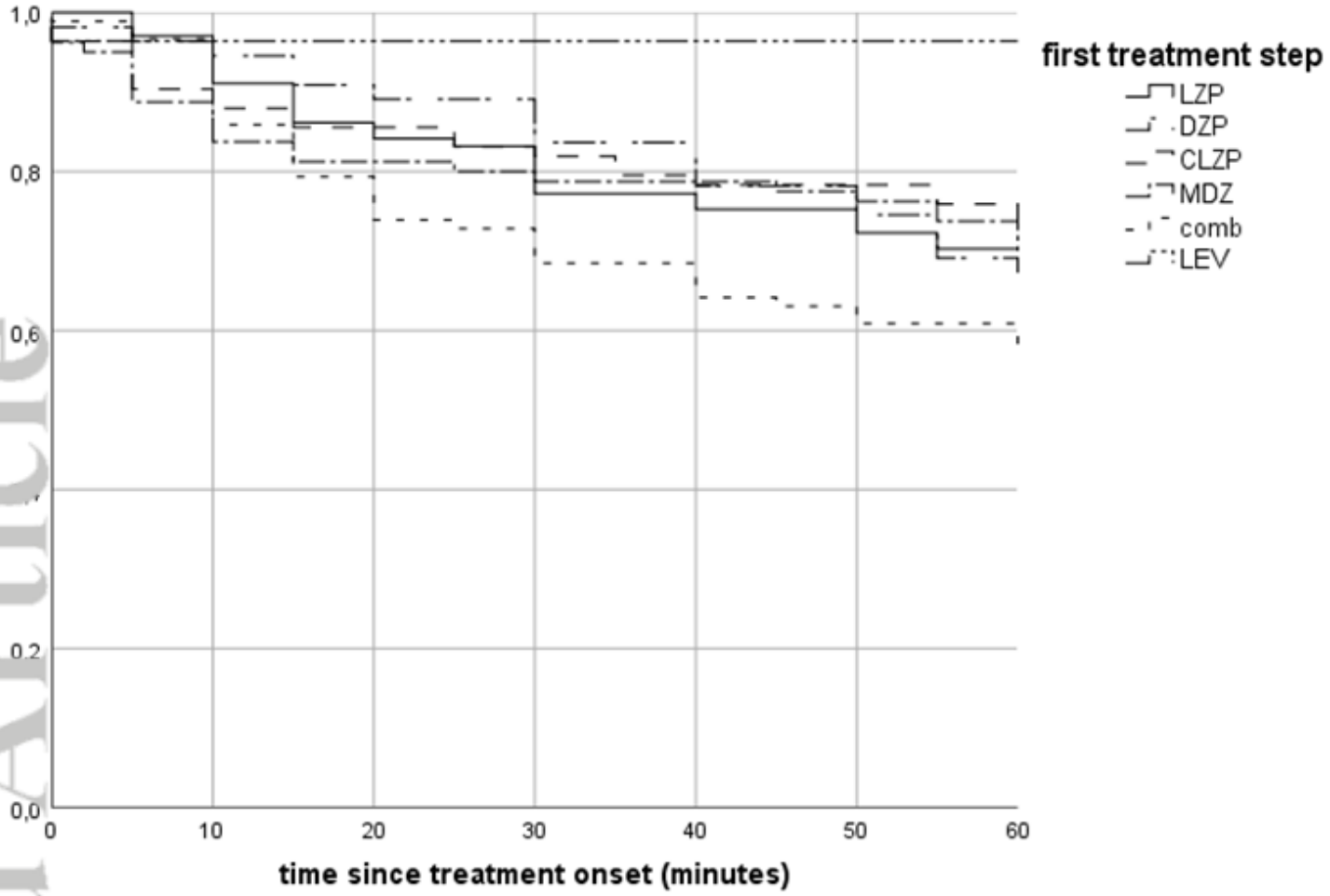

Figure 1b: patients in non-GCSE after treatment onset