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Status epilepticus and benzodiazepine treatment: Use, underdosing and outcome - insights from a retrospective, multicentre registry

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ABSTRACT

Objective: To explore the reasons for and outcomes of non- or undertreatment with benzodiazepines (BZDs) in status epilepticus (SE).
Methods: We retrospectively analysed all SE patients from the urban area of Cologne over two years.
Results: 328 SE patients were eligible, and only 72% were initially treated with BZDs. Of these, only 21.6% were treated sufficiently with BZDs according to current guidelines. SE patients not initially treated with BZDs were significantly older, had less often known epilepsy, had a prolonged arrival time to the emergency room, and presented more often with a non-generalised convulsive semiology. Regarding adequate dosages, patients with a generalised convulsive SE seemed to benefit from a sufficient BZD dosing with significantly shortened mean ventilation duration (37.1 to 208 h), decreased mean intensive care unit (1.7 to 5 days) and in-hospital stay (4.1 to 8.8 days). In contrary, aggressive BZD treatment in non-generalised convulsive SE resulted in a longer inpatient stay (9.2 to 5.8 days) and lower favourable outcome rates at discharge (16% to 63%).
Conclusions: The current SE treatment guidelines for first-line BZD therapy in SE were violated in most patients. Sufficient BZD dosing was beneficial in generalised convulsive SE, but not in other forms of SE. SE semiology might be crucial for treatment decisions with BZDs. Further treatment evidence especially in non-generalised convulsive SE is urgently needed.

1. Introduction

Status epilepticus (SE) represents a frequent neurological emergency with an annual incidence of 10 to 20 per 100,000 inhabitants in Germany and an overall mortality rate of around 9 - 20% [1–3]. It is defined by prolonged seizures or a series of seizures with only an incomplete return of consciousness in between [4]. Although all seizure types can evolve into SE, sufficient treatment evidence exists only for generalised convulsive SE (GCSE) [5,6]. Therefore, the current treatment recommendations refer to this SE form and suggest adopting these recommendations for all other SE forms without further evidence [6,7].

Benzodiazepines (BZDs) are best established as first-line treatments after several randomised controlled trials (RCTs), with equal efficacy throughout this drug class's different substances and application forms [8–13]. However, not all SE patients receive initial BZD therapy in clinical practice, and the reasons for this remain elusive. In the SENSE registry, a prospective multicentre registry for patients with SE from eight centres with particular expertise in SE treatment in German-speaking countries, it was previously shown that BZDs were only given in 86% of GCSE and 73% of non-GCSE. The current guideline's dosage recommendations for BZDs were violated in many cases, leading to reduced dosage applications and prolonged SE duration [14]. Possible explanations for deviations from existing treatment recommendations could be uncertainties as to whether these

Abbreviations: ASM, anti-seizure medication; BZD, benzodiazepine; CCH, City Hospitals Cologne-Merheim; COVID-19, Coronavirus Disease 2019; GCSE, generalised convulsive status epilepticus; HGH, Heilig Geist-Hospital Cologne; ICU, intensive care unit; ILAE, International League Against Epilepsy; mRS, modified Rankin scale; PROSECO, Project for Status Epilepticus in Cologne; RCT, randomised controlled trial; SE, status epilepticus; UHC, University Hospital of Cologne.

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recommendations should be applied to all forms of SE. Besides, treating physicians might fear that higher dosing could lead to relevant side effects such as respiratory depression with the need for intubation and mechanical ventilation.

Guideline violations for first-line BZD treatment in SE appear to be pervasive even in prospective registries and trials [14,15], suggesting a higher proportion in real-world settings and non-specialised centres. This study evaluated the extent and impact as well as possible reasons for refusal of BZD as first-line therapy in SE in a representative cohort of SE patients.

2. Methods

2.1. Patient selection

The *Project for Status Epilepticus in Cologne (PROSECO)* is a collaboration of all Neurology departments in Cologne that provide acute neurological care. *PROSECO* gathers information on adult SE patients. Cologne is the fourth largest city in Germany, with approximately one million inhabitants. All SE patients admitted between 03/2019 and 02/2021 to one of the three hospitals with an acute Neurology department in Cologne were retrospectively analysed. Previously, we addressed and excluded a relevant confounding impact of the Coronavirus Disease 2019 (COVID-19) pandemic during the last year of the observation period [16]. For drop-out handling and detailed epidemiological cohort data, we refer to [16]. This manuscript provides an in-depth analysis of the treatment practice of SE in the registry. The participating hospitals were the University Hospital of Cologne (UHC), the Cologne City Hospitals (CCH), and the Heilig Geist-Hospital Cologne (HGH).

All patients included in this study fulfilled the criteria for SE defined by the International League Against Epilepsy (ILAE) [4], with a seizure duration for GCSE $\geq$ 5 min and non-GCSE $\geq$ 10 min. In the case of generalised convulsive semiology at any timepoint during the SE episode, we labelled the SE as GCSE, otherwise as non-GCSE. The diagnosis for GSCE was made by typical clinical manifestation; in case of non-GCSE, the "Salzburg-EEG-criteria" were used additionally [17]. Patients with hypoxic encephalopathy and an age under 18 years were excluded. For detailed inclusion and exclusion criteria, refer to [16]. The STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines were followed [18].

2.2. Data collection

Data were retrieved from electronic patient files. All SE patients were screened for the following *characteristics*: gender, age, care status before SE, known epilepsy, semiology and aetiology of SE. SE aetiology was defined according to the ILAE proposal for SE classification in acute, remote/progressive or unknown [4]. For *therapy and outcome,* the following parameters were evaluated: initiation of prehospital treatment, drugs used for treatment and their concentrations, the mean number of drugs used, and duration of SE before hospital admission. Refractory SE was defined by the use of >2 anti-seizure therapies. We assessed further need and duration of assisted ventilation, duration of intensive care unit (ICU)-stay, duration of hospitalisation, Status Epilepticus Severity Score (STESS) [19] and modified Rankin-Scale (mRS) at discharge. A favourable outcome was defined as a patient's discharge without a decreased mRS relative to the premorbid level.

2.3. Patient cohorts

First, we divided all SE patients whether they received BZDs as initial therapy. We further analysed the BZD-receiving group for sufficient or underdosed BZD application [20]. Underdosing was defined as less than the dose for a person weighing 50 kg since all SE patients were adults. All groups were assessed for differences in characteristics, therapy and outcome as outlined above.

2.4. Statistical analysis

Statistical analyses were performed using SPSS 28.0 for Windows (IBM, Armonk, New York, USA) and Stata 16.1 software (StataCorp, Texas, USA). For comparisons of categorical independent data, chi-square tests or Fisher's exact tests (if less than 5 items) were performed. T-tests for unpaired variables were performed for comparisons of independent metrical data. All tests were performed two-tailed. Statistically significant different patient and therapy characteristics were further analysed with logistic regression analysis for the primary outcome parameters (dependent variables). P-values <0.05 were estimated as significant.

2.5. Ethics

The local ethics committee of the University of Cologne (21–1443-retro) approved the study. Due to the retrospective design and anonymous data collection, patient consent forms were waived.

3. Results

3.1. Selection process

Our multicentre database search resulted in a total of 485 hits. 157 patients had to be excluded from the analysis: 89 patients did not meet the ILAE-definition criteria for SE [4], five patients had developed SE during their inpatient stay, nine patients were not treated by Neurology departments, another 54 patients had a SE onset outside the urban area of Cologne. The remaining 328 patients were included for further analyses. Of these, 237 (72.3%) received BZDs as initial therapy. The selection process is depicted in **Supplemental material 1**.

3.2. Patient and overall treatment characteristics

The detailed epidemiological data are provided in Table 1. The specific aetiologies of SE are summarised in **Supplemental material 2**. In the 237 (72.3%) SE patients initially treated with BZDs, the most commonly used BZD was midazolam in 123 patients (37.5%), followed by lorazepam in 72 (22%). Rarely used were clonazepam in 13 (4%) and diazepam in 29 patients (8.8%).

Anti-seizure medication (ASM) was the drug of initial choice in 70 patients (21.3%), with levetiracetam being used in 65 patients (19.8%). Four patients were initially treated with lacosamide and one with valproic acid. Only three patients received anaesthetics as first-line treatment (0.9%), two propofol and one thiopental.

3.3. Characteristics of patients with and without BZD treatment

Comparisons between the BZD and the non-BZD group are detailed in Table 2. Patients receiving BZD treatment were younger (mean 61.7 years, to a mean 70 years, p-value **<0.001**), had more often known epilepsy (71.7% to 45.2%, p-value **<0.001**), more often arrived at the emergency department within 30 min after ictal onset (23.6% to 6.8%, p-value **0.002**) and presented more often as GCSE (50.2% to 21.9%, p-value **<0.001**). Prehospital therapy was started in only 14 of the 73 non-BZD patients (19.2%) compared to 155 of the 237 BZD patients (65.4%, p-value: **<0.001**). Notably, the mean number of drugs administered differed in both groups, with less medication in the non-BZD group than in the BZD group (2.2 to 2.7, p-value: **0.005**). SE outcome parameters showed, however, no significant differences between the groups.

3.4. Characteristics of patients with sufficient versus underdosed BZD treatment

The SE patients initially treated with BZDs were further grouped dependant on whether their dosage was sufficient or underdosed per

Table 1
Characteristics, therapy, and outcome of all patients with status epilepticus (SE) ($n = 328$).

Characteristics	
Female, n (%)	150 (45.7)
Age >65 years, n (%)	171 (52.1)
Median age in years (SD, range)	66.4 (18.8, 18.4–93.5)
Admitted	
from home, n (%)	233 (71.0)
from nursing home, n (%)	95 (29.0)
Known epilepsy, n (%)	213 (64.9)
Semiology, n (%)	
GCSE	142 (43.3)
Non-GCSE	186 (56.7)
Aetiology of SE, n (%)	
Acute	37 (11.3)
Remote/progressive	264 (80.5)
Unknown	27 (8.2)
STESS (SD, range)	2.0 (1.5, 0–6)
STESS <2, n (%)	179 (54.6)
Therapy and outcome	
Prehospital initial treatment, n (%)	169 (51.5)
SE duration <0.5 h at arrival, n (%)	65 (19.8)
Initial therapy, n (%)	310 (94.5)
BZD, n (%)	237 (72.3)
MDZ	123 (37.5)
LZP	72 (22.0)
CZP	13 (4.0)
DZP	29 (8.8)
ASM, n (%)	70 (21.3)
LEV	65 (19.8)
Valproic acid	1 (0.3)
Lacosamide	4 (1.2)
Anaesthetic, n (%)	3 (0.9)
Propofol	2 (0.6)
Thiopenthal	1 (0.3)
BZD dosages, n (%)	237 (72.3)
Sufficient	71 (21.6)
Underdosed	162 (49.4)
Unknown	4 (1.2)
Refractory SE (>2 drugs)	134 (40.9)
Median number of drugs (SD, range)	2 (1.4, 0–7)
ICU admission, n (%)	247 (75.3)
Mechanical ventilation, n (%)	49 (14.9)
Median duration ventilation in hours (SD, range)	54.6 (210, 0–921)
Median duration ICU stay in days (SD, range)	1.3 (6.6, 0–63.2)
Median duration in-hospital stay in days (SD, range)	4.3 (11.0, 0.1–103.9)
Favourable outcome at discharge, n (%)	225 (68.6)
Death, n (%)	20 (6.1)

Semiology was defined as generalised convulsive SE (GCSE) or non-GCSE. Therapies were sorted by their drug classes: benzodiazepines (BZD), anti-seizure medications (ASM), and anaesthetics. Abbreviations: MDZ = midazolam, LZP = lorazepam, CZP = clonazepam, DZP = diazepam, LEV = levetiracetam, ICU = intensive care unit, STESS = Status Epilepticus Severity Score. Standard deviation (SD) is provided if applicable.

guideline recommendations [20]. Patient records did not mention initial BZD dosages in four patients (1.2%). Therefore, they were excluded from this part of the analysis.

Only 71 of 233 patients (21.6%) were treated sufficiently according to guideline recommendations with BZDs, while 162 patients (79.4%) were underdosed.

Regarding all SE patients, most treatment and outcome parameters did not differ significantly for sufficient and underdosed BZD patients (see Table 3**a**). Somewhat surprisingly, refractory SE, defined as a need for >2 anti-seizure therapies, was more often seen in the sufficiently treated BZD group (57.7% to 42%, p-value: **0.03**). The mean duration of ventilation was significantly prolonged in the underdosed subgroup (73.9 h compared to 211.3 h, p-value: **0.04**). Prehospital application rate and the number of drugs used did not differ significantly.

As there is still considerable controversy about how aggressive non-GCSE should be treated, and randomised trials are lacking for non-GCSE, we further stratified our cohort for SE semiology (Table 3 **b-c**) [21,22].

Table 2
Status epilepticus (SE) patients with or without benzodiazepine (BZD) treatment were compared for characteristics and outcomes.

	BZD ($n = 237$) n(%)	Non-BZD ($n = 73$) n(%)	Significance
Patient characteristics			
Female, n (%)	109 (46.0)	33 (45.2)	1.0†
Age > 65 years, n (%)	114 (48.1)	48 (65.8)	**0.01**†
Admitted from home, n (%)	160 (67.5)	58 (79.5)	0.06†
Known epilepsy, n (%)	170 (71.7)	33 (45.2)	**<0.001**†
GCSE, n (%)	119 (50.2)	16 (21.9)	**<0.001**†
Aetiology of SE, n (%)			
Acute	24 (10.1)	13 (17.8)	0.1†
Remote/progressive	198 (83.5)	52 (71.2)	
Unknown	15 (6.3)	8 (11.0)	
STESS <2, n (%)	137 (57.8)	34 (46.6)	0.1†
Management and outcome			
Prehospital initial therapy, n (%)	155 (65.4)	14 (19.2)	**<0.001**†
SE onset <0.5 h at arrival, n (%)	56 (23.6)	5 (6.8)	**0.002**†
Refractory SE (>2 drugs)	109 (46.0)	25 (34.2)	0.1†
Mean number of drugs (SD)	2.7 (1.3)	2.2 (1.4)	**0.005**‡
ICU admission, n (%)	182 (76.8)	54 (74.0)	0.6†
Mechanical ventilation, n (%)	39 (16.5)	10 (13.5)	0.6†
Mean duration ventilation in hours (SD)	162.0 (228.3)	61.0 (77.8)	0.2‡
Mean duration ICU stay in days (SD)	3.3 (7.2)	3.0 (5.5)	0.8‡
Mean duration in-hospital stay in days (SD)	6.9 (9.4)	9.4 (15.8)	0.1‡
Favourable outcome at discharge, n (%)	165 (69.6)	45 (61.6)	0.3†
Death, n (%)	14 (5.9)	6 (8.2)	0.6†

Abbreviations: ICU = intensive care unit, GCSE = generalised convulsive SE. Standard deviations (SD) are provided if applicable.
† chi-square test or Fisher's exact test.
‡ *t*-test for unpaired variables.

Stratifications for patient characteristics showed that for GCSE sufficient BZD dosages were withheld in older (>65 years: 17.8% to 48.1%, **p-value 0.001**) and female patients (25% compared to 48.1%, **p-value 0.006**), while no differences were observed in non-GSCE patients (Table 3 **b-c**).

The 77 GCSE patients not treated sufficiently with BZDs had a higher Status Epilepticus Severity Score (STESS) (p-value: **0.01**), less often a refractory SE (24% to 28%, p-value: **0.02**), a prolonged mean ventilation duration (mean 37.1 h compared to 208.6 h, **p-value: 0.01**), stayed significantly longer in the ICU (mean 1.7 days to 5.0 days, **p-value: 0.01**) and had a prolonged mean overall in-hospital stay (4.1 days to 8.8 days, **p-value: 0.003**) compared to GCSE patients who were treated according to current guidelines ($n = 40$). The parameters favourable outcome and mortality rate were comparable for GCSE patients with sufficient or underdosed BZD treatment.

In contrast, the subgroup analysis in patients with non-GCSE showed different results. Whereas most parameter did not differ whether BZD were given in sufficient ($n = 31$) or underdosed dosages ($n = 85$), mechanical ventilation was necessary more often in the sufficiently dosed BZD group (6% to 5%, **p-value: 0.04**). Sufficiently dosed BZD patients also had a prolonged mean in-hospital stay (9.2 days to 5.8 days, **p-value: 0.04**) and less often a favourable outcome at discharge (16% to 63%, **p-value: 0.03**). However, mortality rates were not different.

3.5. Binomial logistic regression analysis for BZD versus non-BZD treatment

In a next step, we aimed at identifying the predictive value of BZD treatment adherence compared to other statistically different patient characteristics in our SE cohort on the outcome parameters by using a binomial logistic regression analysis. For this analysis, the categorial variable "duration of ventilation" was therefore processed to an ordinal

Table 3
a-c Characteristics, therapy, and outcome of sufficiently versus underdosed benzodiazepine (BZD) treated status epilepticus (SE) patients.

Dosage BZD	Sufficient	Underdosed	Significance
a. All SE ($n = 233$)	**$n = 71$**	**$n = 162$**	
Patient characteristics			
Female, n (%)	22 (31.0)	84 (51.9)	**0.004**†
Age > 65 years, n (%)	23 (32.4)	88 (54.3)	**0.003**†
Admitted from home, n (%)	49 (69.0)	108 (66.7)	0.8†
Known epilepsy, n (%)	55 (77.5)	113 (69.8)	0.3†
Aetiology of SE, n (%)			
Acute	5 (7.0)	18 (11.1)	0.2†
Remote/progressive	59 (83.1)	136 (84.0)	
Unknown	7 (9.9)	8 (4.9)	
STESS ≤2, n (%)	47 (66.2)	88 (54.3)	0.1†
Management and outcome			
Prehospital initial therapy, n (%)	49 (69.0)	104 (64.2)	0.6†
SE onset <0.5 h at arrival, n (%)	14 (19.7)	42 (25.9)	0.3†
Refractory SE (>2 drugs), n (%)	41 (57.7)	68 (42.0)	**0.03**†
ICU admission, n (%)	59 (83.1)	120 (74.1)	0.2†
Mechanical ventilation, n (%)	14 (19.7)	25 (15.4)	0.5†
Mean duration ventilation in hours (SD)	73.9 (135.2)	211.3 (256.0)	**0.04**‡
Mean duration ICU stay in days (SD)	2.5 (3.8)	3.7 (8.3)	0.1‡
Mean duration in-hospital stay in days (SD)	6.3 (7.1)	7.2 (10.4)	0.5‡
Favourable outcome at discharge, n (%)	46 (64.8)	117 (72.2)	0.3†
Death, n (%)	1 (1.4)	13 (8.0)	0.1†
b. GCSE ($n = 117$)	**$n = 40$**	**$n = 77$**	
Patient characteristics			
Female, n (%)	10 (25.0)	41 (53.2)	**0.006**†
Age > 65 years, n (%)	7 (17.9)	37 (48.1)	**0.001**†
Admitted from home, n (%)	26 (65.0)	54 (70.1)	0.7†
Known epilepsy, n (%)	29 (72.5)	49 (63.6)	0.4†
Aetiology of SE, n (%)			
Acute	3 (7.5)	11 (14.3)	0.3†
Remote/progressive	33 (82.5)	63 (81.8)	
Unknown	4 (10.0)	3 (3.9)	
STESS ≤2, n (%)	24 (60.0)	26 (33.8)	**0.01**†
Management and outcome			
Prehospital initial therapy, n (%)	36 (90.0)	58 (75.3)	0.1†
SE onset <0.5 h at arrival, n (%)	12 (30.0)	31 (40.3)	0.3†
Refractory SE (>2 drugs), n (%)	24 (60.0)	28 (36.4)	**0.02**†
ICU admission, n (%)	34 (85.0)	62 (80.5)	0.6†
Mechanical ventilation, n (%)	8 (20.0)	20 (26.0)	0.5†
Mean duration of ventilation in hours (SD)	37.1 (39.8)	208.6 (266.5)	**0.01**‡
Mean duration of the ICU stay in days (SD)	1.7 (1.6)	5.0 (10.7)	**0.01**‡
Mean duration in-hospital stay in days (SD)	4.1 (2.7)	8.8 (13.0)	**0.003**‡
Favourable outcome at discharge, n (%)	30 (75.0)	54 (70.1)	0.7†
Death, n (%)	1 (2.5)	3 (3.9)	1†
c. NGCSE ($n = 116$)	**$n = 31$**	**$n = 85$**	
Patient characteristics			
Female, n (%)	12 (38.7)	43 (50.6)	0.3†
Age > 65 years, n (%)	16 (51.6)	51 (60.0)	0.5†
Admitted from home, n (%)	23 (74.2)	54 (63.5)	0.4†
Known epilepsy, n (%)	26 (83.9)	64 (75.3)	0.5†
Aetiology of SE, n (%)			
Acute	2 (6.5)	7 (8.2)	0.8†
Remote/progressive	26 (83.9)	73 (85.9)	
Unknown	3 (9.79	5 (5.9)	
STESS ≤2, n (%)	23 (74.2)	62 (72.9)	1†
Management and outcome			
Prehospital initial therapy, n (%)	13 (41.9)	46 (54.1)	0.3†
SE onset <0.5 h at arrival, n (%)	2 (6.5)	11 (12.9)	0.5†
Refractory SE (>2 drugs), n (%)	17 (54.8)	40 (47.1)	0.5†
ICU admission, n (%)	25 (80.6)	58 (68.2)	0.2†
Mechanical ventilation, n (%)	6 (19.4))	5 (5.9)	**0.04**†
Mean duration ventilation in hours (SD)	122.9 (200.6)	222.4 (236.3)	0.5‡
Mean duration ICU stay in days (SD)	3.5 (5.4)	2.5 (5.0)	0.3‡
Mean duration in-hospital stay in days (SD)	9.2 (9.7)	5.8 (6.9)	**0.04**‡
Favourable outcome at discharge, n (%)	16 (51.6)	63 (74.1)	**0.03**‡
Death, n (%)	0 (0)	10 (11.8)	0.1†

Abbreviations: SE: status epilepticus; STESS: status epilepticus severity score; GCSE: generalised status epilepticus; NGCSE: non-generalised status epilepticus; ICU = intensive care unit. Standard deviation (SD) is provided if applicable.
† chi-square test or Fisher's exact test.
‡ *t*-test for unpaired variables.

form (duration of ventilation ≤ or >24 h) (Fig. 1).

BZD treatment was not predictive of any of the assessed outcome parameters for all SE patients. Favourable outcome at discharge was mainly observed in patients ≤ 65 years (**OR 4.40**) and with a known history of epilepsy (**OR 1.90**). Mechanical ventilation was seen in patients with GCSE semiology (**OR 10.31**). A SE onset <0.5 h at arrival decreased the odds (**OR 3.02**). The odds that SE was refractory decreased with the patient's arrival <0.5 h in the emergency department (**OR 0.48**). None of the analysed variables influenced the duration of ventilation. Further analysis details are given in Fig. 1.

3.6. Binomial logistic regression analysis for sufficient versus underdosed BZD treatment

Analogously, we also assessed the BZD treatment group for the variable sufficient versus underdosed treatment to unmask any dosage-related influences on the outcome parameter (Fig. 2) with comparable results as for the above-mentioned BZD versus non-BZD treatment. The odds for a favourable outcome at discharge were significantly increased with age ≤ 65 years (**OR 5.33**), while no mechanical ventilation was associated with a SE onset <0.5 h before the patient's arrival (**OR 3.06**). The odds for mechanical ventilation increased with a GCSE semiology (**OR 3.16**). Sufficient BZD dosages were associated with a refractory SE (**OR 2.02**). A refractory SE was seen in patients with a delayed arrival after SE onset (**OR 2.18**). Due to the small sample size, binary logistic regression analyses were not applicable for the semiological subgroup.

4. Discussion

Our study offers clinically relevant insights into the current treatment practice and guideline adherence concerning the treatment of adult SE patients in Germany. To this end, we evaluated a representative cohort in the urban area of Cologne encompassed by *PROSECO*.

We show that real-world treatment of SE patients wildly deviates from current treatment guidelines as an initial treatment with BZDs was only performed in 72.3% of all adult SE patients, with a significant proportion of patients being underdosed.

Based on epidemiological data with an annual incidence of 10–20 patients with SE per 100,000 inhabitants in Germany, 200–400 cases were expected for the urban area of Cologne within the assessed two-year period [1]. Our cohort size of 328 patients is within the predicted range, indicating that we explored a representative cohort of adult SE patients.

We confirm prior reports of BZD treatment refusal as first-line therapy in SE in a relevant proportion. In the SENSE registry, a prospective multicentre non-interventional registry of centres with expertise in epilepsy in German-speaking countries, about 20% of SE patients did not receive BZD as a first-line agent [14]. Our study shows that the proportion of SE patients not initially treated with BZDs even increases when different care levels are involved. The reluctance to use BZDs is surprising as their high efficacy and good applicability for SE termination in early stages have been demonstrated in several large prospective trials for prehospital [10,12] and in-hospital management [9,11].

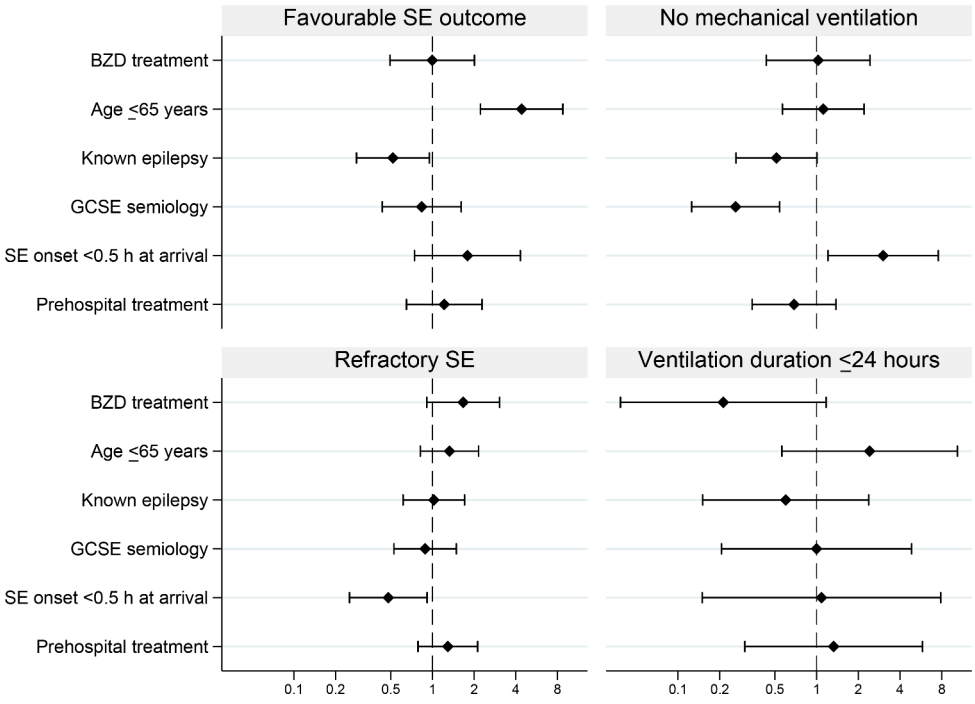

Fig. 1. Binomial logistic regression analysis of all status epilepticus (SE) patients.
Eighteen patients received no therapy and were not included in this analysis. For each of the outcome parameters favourable outcome at discharge, mechanical ventilation and refractory SE, 310 patients were assessed. 39 patients were included for the outcome parameter ventilation duration. The odds ratio and 95% confidence interval on a logarithmic scale is shown. Abbreviations: GCSE = GCSE = generalised convulsive status epilepticus, BZD = benzodiazepine.

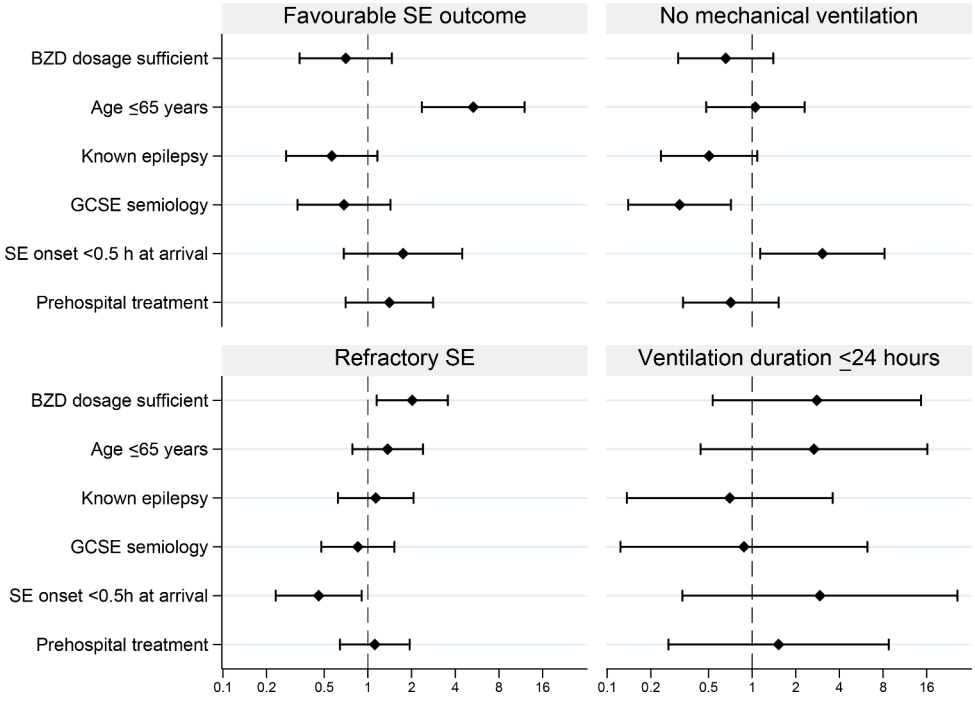

Fig. 2. Binomial logistic regression analysis of all status epilepticus (SE) patients treated with benzodiazepines (BZDs).
The odds ratio and 95% confidence interval on a logarithmic scale are depicted. For favourable outcomes at discharge, mechanical ventilation and refractory SE 237 patients were included. Further, 39 patients were analysed for the outcome parameter ventilation duration. Abbreviation: GCSE = generalised convulsive status epilepticus.

First-line treatment with BZDs was superior to other ASM [9]. Besides, the combination of levetiracetam and clonazepam as initial prehospital SE therapy did not provide treatment benefits, which led to the premature termination of the respective French SAMUKeppra study [23]. Based on this data, BZDs are unequivocally recommended as first-line therapy in SE treatment guidelines [8,20].

The reasons for not using BZDs were not documented in the patient files or emergency service protocols. However, indirect conclusions can be drawn from our epidemiological data, as BZDs were given more frequently in GCSE, in patients with known epilepsy and who were younger. BZD treatment occurred regularly in the prehospital initial therapy setting. This points toward more formally implemented prehospital therapy schemes. As levetiracetam is a listed medication in the ambulances of the Cologne emergency services, its less frequent use in the prehospital setting is not explained by lack of opportunity.

The preference for initial treatment with ASM in elderly patients may point toward a feared respiratory depression due to excessive BZD application, thus influencing treatment decisions. Respiratory depression can occur as an adverse effect, especially in the elderly with opioid comedication [24–26]. Next to polypharmacy, possible reasons include drug accumulation due to prolonged BZD half-life in patients with impaired renal or liver function [27].

Another possible explanation for withholding BZDs is the often challenging diagnosis of a non-GCSE, as no specific clinical or electroencephalographic features exist, especially if epilepsy is not known in the patient history [28]. Furthermore, it is still a matter of debate whether non-GCSE is equally harmful as GCSE regarding cerebral and extracerebral consequences. This, combined with fear of BZD-induced respiratory depression, could have led to preferring ASM in these cases. The most often used ASM was levetiracetam (93% of the cases) in a substantial number of patients (overall 19.8%). SE patients initially treated with ASM were significantly older, had a missing history of epilepsy, and presented more often with a non-GCSE than a GCSE. These parameters are associated with a worse functional outcome in the literature [29–31]. Astonishingly, the significant differences in SE management and patient characteristics in our cohort did not translate into relevant outcome differences.

Not only refusal of BZDs appears to be persistent, also underdosing of BZDs is a well-documented problem in SE treatment [14,15,28], and significant outcome differences might be masked by insufficient BZD treatment observed in different prospective epidemiological studies [14,15]. In our cohort, nearly two-thirds of the patients with SE – if treated with a BZD – did not receive sufficient dosing [8,20]. In a former study, prolonged SE was ascribed to this [14]. By analysing all SE patients who received BZDs for relevant in-hospital and functional outcome parameters, we observed that sufficient BZD treatment of SE patients significantly shortened the mean ventilation time in our cohort. However, other outcome parameter showed no significant differences whether BZDs were dosed adequately or not, as seen in the study by Rossetti et al. [32]. Both Rosetti et al.'s study [32] and ours included large patient groups and were not solely focused on GCSE but also included non-GCSE. Instead, as described by our binary regression analysis, other parameters like age, aetiology and SE severity were strong predictors for functional SE outcome (Figs. 1 and 2). The odds for a favourable SE outcome decreased in the elderly and patients without a known history of epilepsy, while the need for ventilation in SE patients was related to a generalised convulsive semiology and a prolonged arrival time to the hospital. This could misdirect to the hypothesis that treatment deviations from guidelines recommendations have only minor impact on SE outcome.

However, a more detailed look into our SE cohort revealed that SE semiology might be crucial for further treatment decisions. In particular, patients with a GCSE benefited from sufficient dosing as it was significantly associated with a reduced overall duration of ventilation and both ICU and overall in-hospital stay. However, these results should be interpreted with caution as age and gender as possible confounders deviated significantly in this subgroup analysis. Age is a well-described determinant of SE outcome, as described in our regression analysis and in the literature [25,32].

However, the short-term outcome in patients with non-GCSE did not benefit from high dosages of BZD treatment. In contrary, sufficiently dosed patients with non-GCSE had less often a favourable outcome than underdosed patients, suggesting that aggressive BZD treatment could be harmful for non-GCSE patients. There is an ongoing controversy how aggressively non-GCSE should be treated, mainly to the lack of evidence, especially as treatment recommendations are either adapted from GCSE [22] or not covered at all [6,8]. In Cologne, treatment recommendations for non-GCSE are derived from GCSE. Notably, only 11.2% of the 116 non-GCSE patients treated with BZDs arrived within 30 min in the emergency ambulances, compared to 36.8% of the GCSE patients. This suggest that non-GCSE may not be easy to identify and treatment might often be delayed, possibly impacting the outcome. However, there was no statistical difference in arrival time between the non-GCSE patients who were treated sufficiently or who were underdosed (Table 3). Our data indicates that SE semiology might be crucial for treatment decision and that further treatment evidence especially in non-GCSE is urgently needed.

Several limitations of the current study need to be considered. First, this is a retrospective analysis, with no insights into the duration of SE until cessation nor time-to-treatment which both are possible confounders and could have influenced the outcome of SE [4,5,33]. A prospective study design would allow a more detailed assessment of SE treatment. Second, though all neurological emergency departments in Cologne participated in this study, patients treated by other departments or hospitals in Cologne and not directly referred to a neurological emergency department were excluded. This practice could result in a potential underrepresentation of non-GCSE patients. Third, a possible explanation for the missing impact of BZD use and underdosing on SE patient's functional outcome in our cohort is that the compared numbers are too small relative to the effect sizes to be expected, and, therefore, statistically significant effects were masked. Although we cannot provide nationwide epidemiologic data, we consider the study size described to be sufficiently large and representative compared to existing data [32,34,35]. In particular, we combined all levels of care of a region, whereas in previous publications, data were derived from specialised epilepsy centres, which might neglect a relevant number of patients [14]. No long-time follow-up of the patients was provided, and therefore the study could miss any long-term functional outcome changes. Fourth, there are several questions regarding the role of levetiracetam and its effectiveness in SE compared to BZD treatment. A recent study showed a comparable outcome in an RCT pilot study in GCSE patients who received either lorazepam or levetiracetam [36], whereas adjunctive levetiracetam to clonazepam did not show an additional benefit [23]. The role of levetiracetam as an initial treatment of SE seems insufficiently explored to date. Well-designed and adequately powered studies are warranted.

5. Conclusion

In summary, we report real-life data for guideline adherence in an European urban area. Initial BZD therapy in SE was withheld in about a quarter of all cases. This occurred mainly in older patients, non-GCSE, and if the treatment was initiated at the emergency department. Guideline recommendations for BZD dosages were violated in about three of four SE patients. In GCSE, BZD underdosing resulted in prolonged ventilation duration, ICU stay and overall in-hospital stay. However, our data indicate that aggressive BZD treatment might negatively affect the outcome in non-GCSE. Our findings highlight the urgent need for further treatment evidence especially in non-GCSE.

CRediT authorship contribution statement

Felix Kohle: Conceptualization, Data curation, Formal analysis, Methodology, Validation, Visualization, Writing – original draft, Writing – review & editing. **Marie Madlener:** Data curation, Writing – review & editing. **Emanuel F. Bruno:** Data curation, Writing – review & editing. **Gereon R. Fink:** Writing – review & editing. **Volker Limmroth:** Writing – review & editing. **Lothar Burghaus:** Data curation, Writing – review & editing. **Michael P. Malter:** Conceptualization, Data curation, Formal analysis, Methodology, Project administration, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing.

Declaration of Competing Interest

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.seizure.2023.03.020.

References

[1] Knake S, Rosenow F, Vescovi M, Oertel WH, Mueller HH, Wirbatz A, Katsarou N, Hamer HM. Incidence of status epilepticus in adults in Germany: a prospective, population-based study. Epilepsia 2001;42:714–8.
[2] Leitinger M, Trinka E, Giovannini G, Zimmermann G, Florea C, Rohracher A, Kalss G, Neuray C, Kreidenhuber R, Höfler J, Kuchukhidze G, Granbichler C, Dobesberger J, Novak HF, Pilz G, Meletti S, Siebert U. Epidemiology of status epilepticus in adults: a population-based study on incidence, causes, and outcomes. Epilepsia 2019;60:53–62.
[3] DeLorenzo RJ, Hauser WA, Towne AR, Boggs JG, Pellock JM, Penberthy L, Garnett L, Fortner CA, Ko D. A prospective, population-based epidemiologic study of status epilepticus in Richmond, Virginia. Neurology 1996;46:1029–35.
[4] Trinka E, Cock H, Hesdorffer D, Rossetti AO, Scheffer IE, Shinnar S, Shorvon S, Lowenstein DH. A definition and classification of status epilepticus – report of the ILAE task force on classification of status epilepticus. Epilepsia 2015;56:1515–23.
[5] Crawshaw AA, Cock HR. Medical management of status epilepticus: emergency room to intensive care unit. Seizure - Eur J Epilepsy 2020;75:145–52.
[6] Brophy GM, Bell R, Claassen J, Alldredge B, Bleck TP, Glauser T, Laroche SM, Riviello Jr JJ, Shutter L, Sperling MR, Treiman DM, Vespa PM. Guidelines for the evaluation and management of status epilepticus. Neurocrit Care 2012;17:3–23.
[7] van Rijckevorsel K, Boon P, Hauman H, Legros B, Ossemann M, Sadzot B, Schmedding E, van Zandijcke M. Standards of care for non-convulsive status epilepticus: belgian consensus recommendations. Acta Neurol Belg 2006;106:117–24.
[8] Glauser T, Shinnar S, Gloss D, Alldredge B, Arya R, Bainbridge J, Bare M, Bleck T, Dodson WE, Garrity L, Jagoda A, Lowenstein D, Pellock J, Riviello J, Sloan E, Treiman DM. Evidence-based guideline: treatment of convulsive status epilepticus in children and adults: report of the guideline committee of the american epilepsy society. Epilepsy Curr 2016;16:48–61.
[9] Treiman DM, Meyers PD, Walton NY, Collins JF, Colling C, Rowan AJ, Handforth A, Faught E, Calabrese VP, Uthman BM, Ramsay RE, Mamdani MB, Yagnik P, Jones JC, Barry E, Boggs JG, Kanner AM. A comparison of four treatments for generalized convulsive status epilepticus. N Engl J Med 1998;339:792–8.
[10] Alldredge BK, Gelb AM, Isaacs SM, Corry MD, Allen F, Ulrich S, Gottwald MD, O'Neil N, Neuhaus JM, Segal MR, Lowenstein DH. A comparison of lorazepam, diazepam, and placebo for the treatment of out-of-hospital status epilepticus. N Engl J Med 2001;345:631–7.
[11] Leppik lE, Derivan AT, Homan RW, Walker J, Ramsay RE, Patrick B. Double-blind study of Lorazepam and diazepam in status epilepticus. JAMA 1983;249:1452–4.
[12] Silbergleit R, Durkalski V, Lowenstein D, Conwit R, Pancioli A, Palesch Y, Barsan W. Intramuscular versus intravenous therapy for prehospital status epilepticus. N Engl J Med 2012;366:591–600.
[13] Remy C, Jourdil N, Villemain D, Favel P, Genton P. Intrarectal diazepam in epileptic adults. Epilepsia 1992;33:353–8.
[14] Kellinghaus C, Rossetti AO, Trinka E, Lang N, May TW, Unterberger I, Rüegg S, Sutter R, Strzelczyk A, Tilz C, Uzelac Z, Rosenow F. Factors predicting cessation of status epilepticus in clinical practice: data from a prospective observational registry (SENSE). Ann. Neurol. 2019;85:421–32.
[15] Sathe AG, Underwood E, Coles LD, Elm JJ, Silbergleit R, Chamberlain JM, Kapur J, Cock HR, Fountain NB, Shinnar S, Lowenstein DH, Rosenthal ES, Conwit RA, Bleck TP, Cloyd JC. Patterns of benzodiazepine underdosing in the Established Status Epilepticus Treatment Trial. Epilepsia 2021;62:795–806.
[16] Kohle F, Madlener M, Bruno EF, Fink GR, Limmroth V, Burghaus L, Malter MP. Status epilepticus during the COVID-19 pandemic in Cologne, Germany: data from a retrospective, multicentre registry. J Neurol 2022:1–10.
[17] Beniczky S, Hirsch LJ, Kaplan PW, Pressler R, Bauer G, Aurlien H, Brøgger JC, Trinka E. Unified EEG terminology and criteria for nonconvulsive status epilepticus. Epilepsia 2013;54(Suppl 6):28–9.
[18] von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. The strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies. Lancet 2007;370:1453–7.
[19] Rossetti AO, Logroscino G, Milligan TA, Michaelides C, Ruffieux C, Bromfield EB. Status Epilepticus Severity Score (STESS): a tool to orient early treatment strategy. J Neurol 2008;255:1561–6.
[20] Rosenow F, Weber J. Deutsche Gesellschaft für, N. and Österreichische Gesellschaft für, N. S2k guidelines: status epilepticus in adulthood: guidelines of the German Society for Neurology. Nervenarzt 2021;92:1002–30.
[21] Litt B, Wityk RJ, Hertz SH, Mullen PD, Weiss H, Ryan DD, Henry TR. Nonconvulsive status epilepticus in the critically ill elderly. Epilepsia 1998;39:1194–202.
[22] Meierkord H, Boon P, Engelsen B, Göcke K, Shorvon S, Tinuper P, Holtkamp M. EFNS guideline on the management of status epilepticus in adults. Eur J Neurol 2010;17:348–55.
[23] Navarro V, Dagron C, Elie C, Lamhaut L, Demeret S, Urien S, An K, Bolgert F, Tréluyer JM, Baulac M, Carli P. Prehospital treatment with levetiracetam plus clonazepam or placebo plus clonazepam in status epilepticus (SAMUKeppra): a randomised, double-blind, phase 3 trial. Lancet Neurol 2016;15:47–55.
[24] Classen DC, Pestotnik SL, Evans RS, Burke JP. Intensive surveillance of midazolam use in hospitalized patients and the occurrence of cardiorespiratory arrest. Pharmacotherapy 1992;12:213–6.
[25] Uppal P, Cardamone M, Lawson JA. Outcomes of deviation from treatment guidelines in status epilepticus: a systematic review. Seizure 2018;58:147–53.
[26] Midazolam—is antagonism justified? Lancet North Am Ed 1988;332:140–2.
[27] Nordt SP, Clark RF. Midazolam: a review of therapeutic uses and toxicity. J Emerg Med 1997;15:357–65.
[28] Maier S, Godau J, Bösel J, Rösche J. Recognition and treatment of status epilepticus in the prehospital setting. Seizure 2021;86:1–5.
[29] DeLorenzo RJ, Garnett LK, Towne AR, Waterhouse EJ, Boggs JG, Morton L, Choudhry MA, Barnes T, Ko D. Comparison of status epilepticus with prolonged seizure episodes lasting from 10 to 29 min. Epilepsia 1999;40:164–9.
[30] Betjemann JP, Lowenstein DH. Status epilepticus in adults. Lancet Neurol 2015;14:615–24.
[31] Rossetti AO, Logroscino G, Bromfield EB. A clinical score for prognosis of status epilepticus in adults. Neurology 2006;66:1736–8.
[32] Rossetti AO, Alvarez V, Januel JM, Burnand B. Treatment deviating from guidelines does not influence status epilepticus prognosis. J Neurol 2013;260:421–8.
[33] Cheng JY. Latency to treatment of status epilepticus is associated with mortality and functional status. J. Neurol. Sci. 2016;370:290–5.
[34] Vignatelli L, Rinaldi R, Baldin E, Tinuper P, Michelucci R, Galeotti M, de Carolis P, D'Alessandro R. Impact of treatment on the short-term prognosis of status epilepticus in two population-based cohorts. J Neurol 2008;255:197–204.
[35] Aranda A, Foucart G, Ducassé JL, Grolleau S, McGonigal A, Valton L. Generalized convulsive status epilepticus management in adults: a cohort study with evaluation of professional practice. Epilepsia 2010;51:2159–67.
[36] Misra UK, Kalita J, Maurya PK. Levetiracetam versus lorazepam in status epilepticus: a randomized, open labeled pilot study. J Neurol 2012;259:645–8.