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ORIGINAL RESEARCH ARTICLE

Use of Emergency Medication in Adult Patients with Epilepsy: A Multicentre Cohort Study from Germany

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Abstract

Background Emergency treatment with benzodiazepines is indicated in prolonged seizures, seizure clusters and status epilepticus.

Objective The aim of this study was to evaluate the use of emergency medication in adult patients with epilepsy.

Patients and Methods All adult epilepsy patients attending the epilepsy outpatient clinics of the university hospitals in Frankfurt and Marburg in 2015 were asked to participate in this questionnaire-based, retrospective survey.

Results A total of 481 patients with a mean age of 43.4 years (range 18–94 years, 54% female) participated in the study. Among them, 134 patients (27.9%) reported on the prescription of an emergency medication during the last year. Patients receiving emergency medication were younger and exhibited a lower age at epilepsy onset, a higher seizure frequency and a higher number of regularly taken antiepileptic drugs. The most frequently taken emergency drugs were oral lorazepam tablets (65.7%; $n=88$ out of 134), followed by buccal midazolam (23.9%, $n=32$) and rectal diazepam (17.9%, $n=24$). The most common indications for administering the emergency medication were seizures continuing for several minutes (35.1%, $n=47$), but almost the same number of patients (33.6%, $n=45$) stated that the rescue medication was given during or after every seizure. Regarding adverse events, sedation was named as a major (18.7%, $n=25$) or moderate (29.1%; $n=39$) problem by a substantial number of patients. Difficulties in administration were reported by 17 (13%) patients. Two-thirds assessed the efficacy of their emergency medication as good (50.7%, $n=68$) or as very good (15.7%, $n=21$). For multivariate logistic regression analysis, aspects such as young age at onset, active epilepsy, structural etiology, presence of generalised tonic–clonic seizures, past medical history of status epilepticus and living with another person independently predicted prescription of emergency medication.

Conclusions In most cases, unsuitable benzodiazepines with slow absorption due to oral administration were prescribed, or buccal midazolam solution was used off-label in adults. Furthermore, inappropriate use of emergency medication at every seizure was reported by a substantial number of participating patients.

Key Points

Unsuitable benzodiazepines with slow absorption rate or off-label products are frequently used as emergency medication.

In one-third of cases, emergency treatment is probably given without indication, for example after every seizure.

Major efforts should be employed to allow for access to effective and easy-to-apply benzodiazepines that are licensed for treatment, and to educate caregivers regarding appropriate use of emergency benzodiazepines.

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1 Introduction

While most seizures are self-limited and rather short in duration, repetitive and prolonged seizures as well as status epilepticus (SE) require rapid, safe and easy administration of emergency medication. Intravenous benzodiazepines, such as lorazepam, clonazepam or diazepam, are considered the drugs of choice and their efficacy and safety have been proven in different settings [1–4]. Benzodiazepines take effect by binding to a postsynaptic GABA-A receptor and opening a chloride channel, resulting in hyperpolarisation of the postsynaptic neuron [5]. However, intravenous application of benzodiazepines is not feasible for a layperson in an out-of-hospital setting and may even be difficult for healthcare professionals in a patient during a convulsive seizure. Rectal administration of diazepam is an alternative route and has been established for home use for decades [6]. However, rectal emergency treatment is not universally accepted and is associated with negative psychosocial effects, such as embarrassment, social fear, inconvenience in administration and increased stigmatisation [7, 8]. Alternatives include intranasal [5, 9–12] or intramuscular [13, 14] application of benzodiazepines, but these are not commercially available in Germany [15]. Buccal application of midazolam is another established option; however, it has only been approved for children and adolescents in parts of Europe [16–19].

Despite the growing number of studies regarding the efficacy and implications of emergency medication in epilepsy, no studies have been published on real-life prescription patterns of emergency medication in adults. To gain a better understanding of use and access to emergency medication, satisfaction with the application, predictors for prescription and any adverse effects, we surveyed a cohort of adult outpatients at our epilepsy centres over 1 year.

2 Methods

2.1 Study Setting and Design

This non-interventional, multicentre cohort study was performed at the epilepsy outpatient clinics of the university hospitals in Frankfurt am Main (population: 732,688; year 2015; http://www.statistik-hessen.de) and Marburg (73,836; year 2015). Both university hospitals provide the full range of neurological care with expertise in epileptology and intensive care medicine. While Frankfurt serves mainly an urban area, Marburg provides care as the only neurological department for its city and surrounding rural area. Both hospitals provide care for a population of more than one million each. Due to its representative population structure, the area around Marburg was used for a population-based estimate of the incidence of SE and costs due to epilepsy in Germany [20–22]. This study was granted approval by the local ethics committees and registered at the German Clinical Trials Register (DRKS00008885). The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines were followed [23].

2.2 Patients

In spring 2016, we surveyed by mail all patients 18 years of age or older with epilepsy who we treated as outpatients at both epilepsy centres between January 1 and December 31st 2015. The diagnosis and syndrome classification was based on the latest definitions proposed by the International League Against Epilepsy [24, 25]. The treating physician provided information on concomitant diseases and epilepsy syndrome that was determined according to the latest classification. Patients were excluded when the diagnosis of epilepsy could not be determined without doubt. Taking into consideration previous studies, we defined prognostic categories as epilepsy in remission (SR) patients with complete seizure control for ≥ 1 year at the time of study entry; occasional seizures (OCS) patients with persisting seizures who, in the judgment of their physician, did not require treatment changes; active, non-drug-resistant epilepsy (NDRE) patients with recurrent seizures requiring treatment changes and considered by their physician as possibly responsive to treatment changes; and active, drug-resistant epilepsy (DRE) patients with recurrent seizures who, in the judgment of their physician, would not respond to additional treatment changes [26, 27]. Overall, 1340 patients with epilepsy were eligible and were asked for consent and to participate in the study. In total, 485 (36.2%) agreed to participate and returned the questionnaire, while 114 (8.5%) declined. We became aware of the death of eight patients (0.6%, cause of death unknown), while the home address was unknown in 31 patients (2.3%), and 702 patients (52.4%) did not answer the survey. All patients were contacted twice regarding participation in the study. Due to incomplete data, four patients were excluded from analysis, resulting in a study cohort of 481 patients. Among these, 134 patients reported the use and prescription of an emergency medication, while 347 served as the control group.

All participating patients or caregivers provided written informed consent. Data on access to emergency medication, its use, adverse events, current antiepileptic drugs (AEDs), healthcare resource utilisation, housing situation, and quality of life were assessed based on a patient questionnaire examining a 12-month period. Questions regarding use of

emergency medication are provided as electronic supplementary material (ESM). Data on emergency medication and AEDs were cross-checked with patient chart data. Estimation of resource utilisation was validated in earlier studies [21, 28, 29]. QOLIE-31 [30] (Quality of life in epilepsy), NDDI-E [31] (Neurological Disorders Depression Inventory for Epilepsy) and Liverpool adverse events profile [32] were used to estimate quality of life, depression and overall medication side effects. Outcome measures regarding satisfaction with use of emergency medication and side effects were assessed using a four-level Likert scale.

2.3 Data Entry and Statistical Analysis

Statistical analyses were performed using PASW Statistics 22 (SPSS Inc., Chicago, IL, USA) and BiAS. für Windows version 10.01 (epsilon-Verlag, Frankfurt am Main, Germany). Data are presented as mean ± standard deviation (SD), minimum, maximum and median, or percentages and 95% confidence intervals (CI) where appropriate. The Student's *t* test was applied for the comparison of variables with normal distribution and the Mann–Whitney *U* test for comparisons of variables with non-normal distribution. Chi square tests were performed to assess the distribution of patients with and without use of emergency medication. For definition of factors delineating patients taking or not taking emergency medication (Table 1) the Holm–Bonferroni method was used to counteract the problem of multiple comparisons. In addition to descriptive statistics, we examined which factors were independently associated with prescription of emergency medication at all. Therefore, clinical variables were specified based on the results of the univariate analysis. Using multivariate logistic regression, we examined whether age, age at onset of epilepsy, seizure frequency, prognostic group, etiology, seizure semiology, history of SE, AED treatment and housing situation influenced the prescription of emergency medication. All *p* values were two-sided; values < 0.05 were regarded as statistically significant.

3 Results

3.1 Patient Cohort

In total, 481 patients participated in this study, and their mean age was 43.4 years (standard deviation [SD] 16.7, range 18–94); 53.6% ($n = 258$) were female. The distribution of age ($p = 0.171$) and gender ($p = 0.315$) did not differ across the two epilepsy centres. In total, 60.7% ($n = 292$) of the patients had active epilepsy with at least one seizure within the last 12 months, whereas 39.3% ($n = 189$) were in remission without seizures for > 1 year. A majority of 75.7% ($n = 364$) had structural-metabolic focal epilepsy, the remaining had genetic generalised epilepsy (16.4%, $n = 79$), structural generalised epilepsy and epileptic encephalopathies (2.9%, $n = 14$) or an unclear epilepsy syndrome (4.8%, $n = 23$). Only one patient (0.2%) had self-limiting focal epilepsy. A history of SE was present in 16.0% of the patients ($n = 77$). On average, epilepsy onset was at the age of 25.5 years (SD 19.6, range 0–85). At the time of the study entry, the mean disease duration was 17.4 years (SD 14.7, range 0–68). Patients were taking a mean number of 1.7 AEDs (SD 0.9, range 0–5). Slightly more than half of the patients received anticonvulsant polytherapy (51.1%, $n = 246$), 46.6% ($n = 224$) a monotherapy and 2.3% ($n = 11$) did not take any AEDs. The most frequently prescribed AEDs were levetiracetam (45.5%, $n = 220$), lamotrigine (36.0%, $n = 173$) and valproate (22.7%, $n = 109$); for details of AEDs prescription please refer to Supplementary Table S1 (see ESM).

3.2 Characteristics of Patients Using Emergency Medication

In total, 134 patients (27.9%) reported the use and prescription of an emergency medication during the last year. Table 1 provides characteristics of patients receiving and patients not receiving emergency medication. Overall, patients receiving emergency medication were significantly younger, exhibited a lower age at epilepsy onset, a higher seizure frequency and a higher number of regularly taken AEDs. More patients receiving emergency medication were using a seizure calendar, they were more often in outpatient care due to epilepsy, and the proportion of patients with active epilepsy was larger. There was no difference in gender distribution, epilepsy duration, depression and adverse events. Regarding the QOLIE-31 questionnaire, the two groups differed in the overall score with lower values indicating a poorer quality of life in patients receiving emergency medication. In three of seven subcategories, they scored worse regarding seizure worry, medication effects and social functioning.

3.3 Use of Emergency Medication

The most frequently prescribed emergency medications were oral lorazepam tablets (65.7%; $n = 88$ out of 134), followed by buccal midazolam (23.9%; $n = 32$) and rectal diazepam 17.9% ($n = 24$). Oral clonazepam (3.7%; $n = 5$), oral diazepam (3.7%; $n = 5$), oral clobazam (3%; $n = 4$) and intranasal midazolam (1.5%; $n = 2$) were prescribed less frequently. Oral alprazolam, oral chloral hydrate, intramuscular diazepam and rectal phenytoine were only used in single cases. For details regarding dosing and number of applications during the past 3 months please refer to Table 2.

A majority of 61.2% ($n = 82$) reported that the emergency medication was administered by relatives. In one out

Table 1 Characteristics of patients receiving and not receiving emergency medication

Characteristics	Emergency medication $n=134$	No emergency medication $n=347$	p value
Age			
Mean in years ± SD	40.1 ± 17.6	44.7 ± 16.3	0.001*
Range	18–94	18–86	
Gender			
Female	76 (56.7%)	182 (52.4%)	0.4
Male	58 (43.3%)	165 (47.6%)	
Age at epilepsy onset			
Mean in years ± SD	21.9 ± 20.6	26.9 ± 19.1	0.001*
Range	0–85	0–81	
Epilepsy duration			
Mean in years ± SD	18.0 ± 14.5	17.2 ± 14.9	0.29
Range	0–68	0–61	
Seizure frequency			
≥ 1/day	13 (9.7%)	16 (4.6%)	< 0.001*
≥ 1/week	16 (11.9%)	37 (10.7%)	
≥ 1/month	31 (23.1%)	39 (11.2%)	
≥ 1/6 months	18 (13.4%)	36 (10.4%)	
≥ 1/year	11 (8.2%)	18 (5.2%)	
None for > 1 year	31 (23.1%)	158 (45.5%)	
Persisting, frequency unclear	14 (10.4%)	43 (12.4%)	
Prognostic group			
Seizure remission	31 (23.1%)	158 (45.5%)	< 0.001*
Occasional seizures	19 (14.2%)	41 (11.8%)	
Active, non-drug refractory	35 (26.1%)	90 (25.9%)	
Active, drug refractory	49 (36.6%)	58 (16.7%)	
Etiology/epilepsy syndrome			
Genetic generalised	13 (9.7%)	66 (19%)	0.007
Structural generalised and epileptic encephalopathies	11 (8.2%)	3 (0.9%)	
Self-limiting focal	0 (0%)	1 (0.3%)	
Structural-metabolic focal	107 (79.9%)	257 (74.1%)	
Unclear	3 (2.2%)	20 (5.8%)	
Number of AEDs			
Mean ± SD	2.1 ± 1.0	1.6 ± 0.8	< 0.001*
Range	0–5	0–5	
No AEDs	1 (0.7%)	10 (2.9%)	< 0.001*
Monotherapy	41 (30.6%)	183 (52.7%)	
2 AEDs	52 (38.8%)	105 (30.3%)	
≥ 3 AEDs	40 (29.9%)	49 (14.1%)	
NDDI-E depression			
Yes	25 (18.7%)	81 (23.3%)	0.465
No	76 (56.7%)	196 (56.5%)	
NA	33 (24.6%)	70 (20.2%)	
NDDI-E sum			
Mean ± SD	11.7 ± 3.9	11.4 ± 4.4	0.407
Range	6–23	6–23	
LAEP sum			
Mean ± SD	40.0 ± 9.7	38.6 ± 11.4	0.109
Range	19–62	19–72	

Table 1 (continued)

Characteristics	Emergency medication $n=134$	No emergency medication $n=347$	p value
QOLIE-31 seizure worry			
Mean ± SD	50.2 ± 10.6	52.7 ± 11.3	0.011
Range	27.4–66.2	27.4–66.2	
QOLIE-31 overall quality of life			
Mean ± SD	46.8 ± 10.2	48.1 ± 11.1	0.22
Range	20.3–67.9	13.6–67.9	
QOLIE-31 emotional well-being			
Mean ± SD	48.0 ± 9.7	48.5 ± 10.3	0.62
Range	23.4–64.9	21.4–67.0	
QOLIE-31 energy/fatigue			
Mean ± SD	46.0 ± 9.0	48.0 ± 10.0	0.075
Range	23.8–64.1	23.8–71.2	
QOLIE-31 cognitive functioning			
Mean ± SD	48.0 ± 11.7	49.0 ± 11.8	0.351
Range	23.7–67.6	23.7–67.6	
QOLIE-31 medication effects			
Mean ± SD	49.9 ± 8.8	52.3 ± 9.6	0.011
Range	31.9–64.6	31.9–64.6	
QOLIE-31 social functioning			
Mean ± SD	46.6 ± 10.6	49.4 ± 10.9	0.005
Range	25.0–62.2	25.0–62.2	
QOLIE-31 overall score			
Mean ± SD	46.1 ± 11.9	48.9 ± 12.5	0.033
Range	11.5–70.5	20.3–72.1	
Visual analogue scale			
Mean ± SD	59.5 ± 21.1	62.1 ± 23.2	0.145
Range	10.0–100.0	0.0–100.0	
Outpatient treatment in the past 3 months			
Yes	47 (35.1%)	66 (19%)	< 0.001*
No	84 (62.7%)	275 (79.3%)	
NA	3 (2.2%)	6 (1.7%)	
Inpatient treatment in the past 3 months			
Yes	20 (14.9%)	26 (7.5%)	0.012
No	114 (85.1%)	321 (92.5%)	
Seizure diary			
Yes	67 (50%)	107 (30.8%)	< 0.001*
No	67 (50%)	240 (69.2%)	
Housing situation			
Alone	25 (18.7%)	97 (28%)	0.036
With others	109 (81.3%)	250 (72%)	

AED antiepileptic drug, *LAEP* Liverpool adverse events profile, *NA* not available, *NDDI-E* Neurological Disorders Depression Inventory for Epilepsy, *QOLIE* Quality of Life in Epilepsy, *SD* standard deviation

*Significant p values after Holm–Bonferroni correction

of four patients, the emergency medication was administered by themselves (24.6%, $n=33$). Friends or colleagues (14.9%, $n=20$), and formal caregivers (7.4%, $n=10$) were also reported. Oral lorazepam was administered by patients themselves in 28% of the cases while this was the case for buccal midazolam in one and for rectal diazepam two patients.

Table 2 Details of emergency prescriptions and administration

	$N=134$	Dosage (mg) mean ± SD	Minimum (mg)	Median (mg)	Maximum (mg)	Applications[a] mean ± SD
Lorazepam oral	88 (65.7%)	1.6 ± 0.8	0.5	1	5	1.6 ± 3.5
Midazolam buccal	32 (23.9%)	7.5 ± 2.8	2.5	10	10	1.5 ± 2.7
Diazepam rectal	24 (17.9%)	10.2 ± 7.5	2	10	40	1.8 ± 2.6
Clonazepam oral	5 (3.7%)	2.7 ± 1.2	2	2	4	14.3 ± 20.6
Diazepam oral	5 (3.7%)	6.0 ± 2.9	2.5	5	10	0.5 ± 0.7
Clobazam oral	4 (3%)	11.3 ± 6.3	5	10	20	6.0 ± 5.7
Midazolam intranasal	2 (1.5%)	5.0 ± 0.0	5	5	5	3.0 ± 2.8
Alprazolam oral	1 (0.7%)	1				12
Chloral hydrate oral	1 (0.7%)	500				1
Diazepam IM	1 (0.7%)	10				3
Phenytoin rectal	1 (0.7%)	100				2

IM intramuscular, *SD* standard deviation

[a]Number of applications in the past 3 months

Almost three quarters of the patients (73.1%, $n=98$) stated that they have 24/7 access to emergency medication throughout the day and night, 14 patients (10.4%) indicated access from 4 to 8 h per day, two patients (1.5%) up to 4 h per day, and three patients (2.2%) indicated that they only have access at night. Emergency medication was usually kept at home (64.9%, $n=87$) and was carried on their person or in a bag (53.7%, $n=72$). Fewer patients reported storing the medication at work or at school (17.9%, $n=24$), with relatives (2.2%, $n=3$) or in the car (1.5%, $n=2$).

Seizures continuing for several minutes (35.1%, $n=47$), seizure clusters (20.1%, $n=27$), auras (9.7%, $n=13$), unusually severe seizures (1.4%, $n=2$), loss of consciousness (0.7%, $n=1$) and cyanosis (0.7%, $n=1$) were named as indications to administer emergency medication. A large proportion (33.6%, $n=45$) stated they administered the emergency medication for every seizure, either during seizure activity or shortly afterwards.

Regarding adverse events associated with emergency medication, sedation was named as a major (18.7%, $n=25$) or moderate (29.1%; $n=39$) problem by a substantial number of patients. Reported major or moderate sedation did not differ between oral lorazepam ($n=45/68$; 66.2%, $p=0.065$), buccal midazolam ($n=8/20$; 40%) and rectal diazepam ($n=14/19$; 73.7%, $p=0.07$). Dizziness, anxiety and pain were reported less frequently; for details please refer to Fig. 1. No problems with administration of emergency medication were reported by the majority of 66.4% ($n=89$), while 12.7% ($n=17$) reported difficulties such as trickling, spitting out or vomiting the medication. In particular, inserting the medication into the patient's mouth during a seizure was named as a major issue (6.7%, $n=9$). Reported difficulties in administration did not differ between oral lorazepam ($n=11/72$; 15.3%), buccal midazolam ($n=4/24$; 16.7%; $p=1.0$) and rectal diazepam ($n=5/19$; 26.3%, $p=0.432$). Most patients assessed the efficacy of their emergency medication as good (50.7%, $n=68$) or very good (15.7%, $n=21$), whereas 11.9% ($n=16$) evaluated the efficacy as low and 1.5% ($n=2$) as very low. Reported good or very good efficacy did not differ between oral lorazepam ($n=60/72$; 83.3%), buccal midazolam ($n=22/24$; 91.7%; $p=0.504$) and rectal diazepam ($n=17/20$; 85%, $p=1.0$).

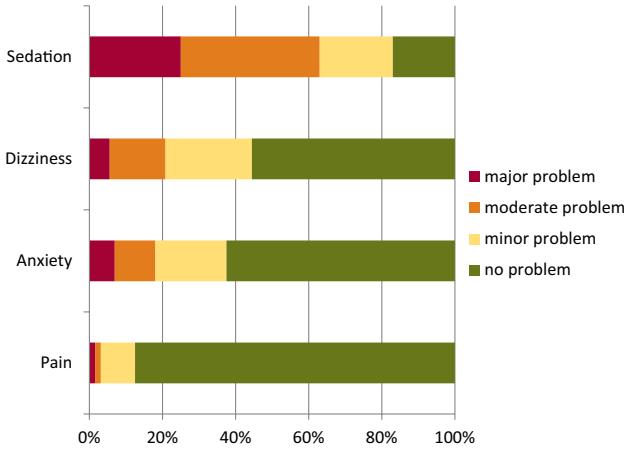

Fig. 1 Adverse events reported with use of emergency medication. Colours represent grading of severity, which may be subject to patients' recall-bias (four-level Likert scale; *y*-axis: adverse event; *x*-axis: percentage of patients)

Table 3 Predicting factors for the prescription of emergency medication

Predicting factors	Emergency medication $n=134$	No emergency medication $n=347$	Univariate OR (95% CI)	p value	Multivariate OR (95% CI)	p value
Age at onset						
< 18 years	75 (56%)	130(37.5%)	2.13 (1.41–3.23)	<0.001	2.14 (1.28–3.57)	0.004
≥ 18 years	53 (39.6%)	196 (56.5%)				
NA	6 (4.5%)	21 (6.1%)				
Active epilepsy						
Yes	103 (76.9%)	189 (54.5%)	2.78 (1.77–4.37)	<0.001	1.82 (1.01–3.26)	0.046
No	31 (23.1%)	158 (45.5%)				
Seizure frequency						
< 1/month	69 (51.5%)	251 (72.3%)	2.49 (1.65–3.76)	<0.001	0.96 (0.47–1.94)	0.899
≥ 1/month	65 (48.5%)	95 (27.4%)				
Prognostic group						
Drug resistant	49 (36.6%)	58 (16.7%)	2.87 (1.83–4.51)	<0.001	1.25 (0.60–2.61)	0.556
Non-drug resistant	85 (63.4%)	289 (83.3%)				
Etiology						
Genetic or unclear	16 (11.9%)	87 (25.1%)	2.47 (1.39–4.39)	0.001	2.86 (1.46–5.62)	0.002
Structural-metabolic	118 (88.1%)	260 (74.9%)				
GTCS						
Yes	59 (44%)	89 (25.6%)	2.28 (1.51–3.46)	<0.001	2.00 (1.15–3.49)	0.014
No	75 (56%)	258 (74.4%)				
Falls						
Yes	100 (74.6%)	195 (56.2%)	2.29 (1.47–3.57)	<0.001	1.68 (0.95–2.98)	0.075
No	34 (25.4%)	152 (43.8%)				
Loss of consciousness						
Yes	69 (51.5%)	150 (43.2%)	1.39 (0.94–2.08)	0.125		
No	65 (48.5%)	197 (56.8%)				
Nocturnal						
Yes	17 (12.7%)	50 (14.4%)	0.86 (0.48–1.56)	0.663		
No	117 (87.3%)	297 (85.6%)				
Automotor						
Yes	42 (31.3%)	77 (22.2%)	1.60 (1.03–2.50)	0.045	1.21 (0.71–2.05)	0.487
No	92 (68.7%)	270 (77.8%)				
Aura						
Yes	66 (49.3%)	137 (39.5%)	1.49 (1.00–2.22)	0.064		
No	68 (50.7%)	210 (60.5%)				
Status epilepticus						
Yes	36 (26.9%)	41 (11.8%)	2.74 (1.66–4.53)	<0.001	1.93 (1.08–3.47)	0.027
No	98 (73.1%)	306 (88.2%)				
AEDs						
Monotherapy or no AED	42 (31.3%)	193 (55.6%)	2.75 (1.80–4.19)	<0.001	1.48 (0.88–2.49)	0.142
Polytherapy	92 (68.7%)	154 (44.4%)				
Housing situation						
Alone	25 (18.7%)	97 (28%)	1.69 (1.03–2.77)	0.036	1.90 (1.07–3.39)	0.03
With partner, relatives or nursing home	109 (81.3%)	250 (72%)				

AED antiepileptic drug, *CI* confidence intervals, *GTCS* generalised tonic–clonic seizure, *NA* not available, *OR* odds ratio

3.4 Predictors for Prescription of Emergency Medication

According to univariate analysis, several factors presented in Table 3 were associated with an increased likelihood that patients had been prescribed an emergency medication. Age and seizure characteristics, such as loss of consciousness, nocturnal seizures and aura, did not influence prescription of emergency medication.

For multivariate logistic regression analysis, aspects such as young age at onset of epilepsy, active epilepsy, symptomatic etiology, presence of generalised tonic–clonic seizure (GTCS), past medical history of SE and housing situation with presence of another person independently predicted prescription of emergency medication.

4 Discussion

This multicentre study is the first evaluation of real-world emergency treatment in adult patients with epilepsy regarding the type of prescribed medication, its use, tolerability and patient satisfaction.

Despite the growing number of studies regarding the efficacy and safety of emergency medication [14–18], no studies have been published to date evaluating the prescription patterns of emergency medication in adults. However, this remains an essential issue, in particular since published clinical guidelines are mostly limited to the hospital setting and offer few recommendations for out-of-hospital settings. Furthermore, a recent study regarding out-of-hospital treatment of SE shows deficits in recognition of non-convulsive SE resulting in delay of appropriate treatment [33]. Therefore, insight into the actual practice regarding prescription and utilisation of emergency medication might support the development of more efficient, patient-oriented prescriptions and application guidelines.

Overall, there appears to be a heterogeneous prescription pattern with, in part, unsuitable benzodiazepines. Oral lorazepam (65.7%, brand name: Tavor expidet, sublingual tablets) was the most frequently prescribed emergency medication, which should not be used as first choice in SE due to the slow absorption rate if swallowed or melted in the mouth [34, 35]. The second most frequently prescribed emergency medication was buccal midazolam (23.9%), even though it has only been approved for children and adolescents in Germany [16–18]. Rectal diazepam ranks third (17.9%) and is the only licensed option for prolonged seizures and SE. Its limited use is probably explained by embarrassment and stigmatisation of patients due to the rectal route [7, 8]. Furthermore, various benzodiazepines with different formulations and application routes, such as oral clonazepam (3.7%), oral diazepam (3.7%), oral clobazam (3%), intranasal midazolam (1.5%), oral alprazolam (0.7%), oral chloral hydrate (0.7%) and intramuscular diazepam (0.7%), were used in patients as emergency medications. This is worrying, as these preparations are neither evidence-based nor licensed for use in prolonged seizures or SE. Use of oral benzodiazepine preparations may be justified to avoid or ameliorate a cluster of focal seizures or to abort a prolonged focal seizure. However, use in seizure-free patients and overuse may lead to development of tolerance [36].

Contrary to these findings is the high patient satisfaction reported in our survey. The majority of 66.4% reported no difficulties in administration of emergency medication and most patients assessed the efficacy of their emergency medication as good (50.7%) or even very good (15.7%). The diverging judgment between expert opinion and patients' view may be due to the anxiolytic properties of benzodiazepines and the circumstances in which emergency medication is used. Administration of emergency medication was reported in seizures continuing for several minutes (35.1%) and seizure clusters (20.1%) on the one hand, but also for every seizure (33.6%), either during seizure activity or shortly afterwards. In the latter case, seizures would probably resolve by themselves as studies show that convulsive seizures rarely exceed 2 min of duration while focal complex seizures remain well below 7 min [37]. Such application after every seizure may be appropriate for treatment of seizure clusters, if seizures are mild or distributed over hours or days. Only three quarters of the patients stated that they had 24/7 access to the emergency medication, which is worrisome as seizures are usually not limited to certain time periods.

Independent predictors of the prescription of emergency medication were young age at epilepsy onset, which might be due to different prescription patterns in the neuropediatric setting, and a housing situation with presence of another person, usually parents in the younger age group. Presence of active epilepsy, symptomatic etiology, GTCS and past medical history of SE reflect a severe course of disease, justifying prescription of emergency medication. Patients with refractory focal epilepsy and seizure clustering are known to be at higher risk for convulsive SE [38].

The strength of this study is its ability to provide a realistic view on the prescription, use, tolerability and patient satisfaction with emergency medication in adult patients with epilepsy. However, due to the retrospective design, this study has inherent weaknesses. We used patient questionnaires to collect data regarding the use of emergency medication and the possibility of incomplete or wrong patient recall in some of the surveyed categories cannot be excluded. In addition, patients may tend to report a better effect of emergency medication to maintain their perceived self-efficacy. Sedation as a result of emergency medication might be difficult to delineate from postictal altered consciousness. Furthermore,

we did not assess cognitive impairment in detail in our study as a predicting factor, and patients with cognitive impairment might get neglected in studies requiring the return of questionnaires. Future studies should assess who is prescribing emergency medication and if treatment protocols are in place. Both could influence prescription patterns and administration of emergency medication. German national guidelines do not advise in detail on emergency medication use in seizure clusters and prolonged seizures. Based on a survey from Cornwall, Shankar et al. argue that training should facilitate safe, person-centred care and appropriate administration of rescue medication to people with epilepsy, and stress the need for comprehensive guidelines [39].

Access to effective and easily applicable benzodiazepines is difficult for adults with epilepsy in need of emergency medication, and their neurologists. Besides buccal midazolam, which is not approved for adults, further alternatives might be nasal or intramuscular midazolam. Nasal midazolam spray is easy to apply and can be delivered from any position. Even during a seizure, it only takes a little time to administer the dose, and patients do not need to be restrained. These findings are in line with caregivers' and patients' opinions from multiple studies [9–11], indicating that intranasal midazolam was easier to use than rectal diazepam. RAMPART (the Rapid Anticonvulsant Medication Prior to Arrival Trial) [14] demonstrated the importance of reliable and rapid administration of midazolam in SE. The chosen early administration of intramuscular midazolam compared with intravenous lorazepam was the best option for the prehospital treatment of SE by paramedics [14]. The authors concluded that the RAMPART results supported nonintravenous midazolam administration [40]. Furthermore, delayed treatment of SE might lead to refractory SE with need for anaesthesia associated with increased morbidity and mortality [41]. Therefore, major efforts should be made to afford access to effective and easily applicable benzodiazepines for adults. Oromucosal midazolam was shown to be cost effective for the treatment of prolonged acute convulsive seizures in children. It was also evaluated in adolescents in the context of treatment pathways in seven European countries [17, 42]. An efficacy and effectiveness advantage over rectal diazepam and other medications, such as buccal lorazepam and unlicensed buccal midazolam, was found [42]. This is reflected by the current NICE guidelines [43] that recommend prescription of buccal midazolam or rectal diazepam for use in the community for children, young people and adults who have had a previous episode of prolonged or serial convulsive seizures. While there may be divergence between licensed indication and published studies and patient views, this does not automatically translate to a divergence between expert opinion and patient views. Physicians prescribing buccal midazolam in adults may face reimbursement issues by the statutory health insurance in Germany. Furthermore, in case of complications, using a non-licensed medication may be of disadvantage in medical liability cases.

5 Conclusions

Among adults with epilepsy that participated in this survey, emergency seizure treatment is independently associated with the following five clinical factors: (1) structural etiology; (2) age of epilepsy onset; (3) history of GTCS; (4) SE; and (5) not living alone. Currently, unsuitable benzodiazepines with slow absorption rates or off-label products are frequently used. In one-third of the cases, emergency treatment is probably given without an indication, such as after every seizure. This may lead to overuse or development of tolerance. Major efforts should be made to allow for access to effective and easy-to-apply benzodiazepines that are licensed for the treatment of prolonged seizures or SE and to inform and educate caregivers regarding the indication of emergency benzodiazepines.

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Compliance with ethical standards

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