CNS Drugs (2023) 37:993–1008
https://doi.org/10.1007/s40263-023-01049-w

ORIGINAL RESEARCH ARTICLE

Trends and Differences in Status Epilepticus Treatment of Children and Adults Over 10 Years: A Comparative Study of Medical Records (2012–2021) from a University Hospital in Germany

Leonore Purwien[1,2] · Susanne Schubert-Bast[1,2,3] · Matthias Kieslich[1,2,3] · Michael W. Ronellenfitsch[2,4,5] · Michael Merker[3] · Marcus Czabanka[6] · Laurent M. Willems[1,2] · Felix Rosenow[1,2] · Adam Strzelczyk[1,2]

Accepted: 25 October 2023 / Published online: 18 November 2023
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Abstract

Background and Objectives Over the last decade, significant advancements have been made in status epilepticus (SE) management, influenced by landmark trials such as ESETT and RAMPART. The objectives of this study were to explore the evolution of drug treatments for patients with SE, to investigate its association with outcomes and mortality, and to evaluate differences in treatment patterns between adults and children for a potential shift in medication trends due to the above mentioned trials.

Methods The medical records of patients with SE treated at University Hospital Frankfurt between 2012 and 2021 were evaluated for medication trends and outcomes. Children and adults were analyzed separately and jointly.

Results This study included 1151 SE episodes in 1021 patients (mean age = 53.3 ± 28.3 years; 52.5 % female [$n = 533$]). The overall percentage of patients with SE treated prehospital was stable over the last decade. More than half (53.6 %) of children were treated prehospital, compared with less than one-third (26.7 %) of adults. Prehospital midazolam use increased over time, while diazepam use decreased. Lorazepam was the most commonly used benzodiazepine in hospitals in 2012–2013, used in 40.8 % of all episodes. However, its use declined to 27.2 % in 2020–2021, while midazolam use increased to 44.0 %. While the use of older antiseizure medications (ASMs) such as phenobarbital ($p = 0.02$), phenytoin ($p < 0.001$), and valproate ($p < 0.001$) decreased, the use of newer ASMs such as levetiracetam and lacosamide significantly increased ($p < 0.001$). Propofol and continuous midazolam infusion remained the most used third-line therapy drugs. Overall mortality was 16.5 % at discharge and 18.9 % at 30 days. Mortality rates did not change between 2012 and 2021.

Conclusion Midazolam has become the preferred benzodiazepine in pre- and in-hospital settings, both in children and adults. The same applies to the increased use of levetiracetam and lacosamide over time in children and adults, while phenobarbital, phenytoin, and valproate use decreased. Continuous midazolam infusion and propofol remain the most frequently used anesthetic drugs. Mortality and outcome remain stable despite changes in medication patterns.

1 Introduction

Status epilepticus (SE) is a frequent neurological emergency occurring in patients of all ages. The incidence of SE ranges from 10 to 20/100,000 in Germany and is highest in patients aged > 60 years and in young children [1–3]. Status epilepticus is associated with high morbidity and mortality—increasing with refractoriness—and requires immediate medical treatment [4–9].

The latest SE treatment recommendations advise a three-stage strategy for children and adults. Appropriate benzodiazepines such as lorazepam, clonazepam, diazepam, or midazolam are initially given at sufficiently high doses [7, 8, 10–12]. Recent studies have shown the superiority of intramuscular (IM) midazolam over intravenous (IV) lorazepam and the noninferiority of intranasal or buccal midazolam over IV diazepam, while IV lorazepam or diazepam has historically been the standard of care [13–16].

When benzodiazepines are unsuccessful in terminating SE or preventing SE recurrence, antiseizure medications (ASMs) are used as second-line therapy [7, 8, 10–12]. Until the 1990s, only phenobarbital, phenytoin, and later valproate were available as IV agents. Over the last two decades, levetiracetam, lacosamide, and brivaracetam have become available as IV agents. However, none are licensed for treating SE [10, 17, 18]. Current studies indicate newer ASMs are as effective in SE treatment but have fewer adverse effects and interactions than older ASMs [16, 19–23]. When

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Key Points

The percentage of patients given prehospital SE treatment did not change during the study period.

Midazolam has become the most frequently used benzodiazepine for pre- and in-hospital SE treatment in children and adults.

The use of newer ASMs, such as levetiracetam and lacosamide, increased significantly in children and adults.

The overall use of older ASMs, such as phenytoin and valproate, decreased significantly.

Continuous midazolam infusion and propofol remain the most frequently used anesthetic drugs.

Outcome and mortality did not change over the study period.

ASMs also fail to terminate SE, anesthetics may become necessary in a third therapy step [7, 8, 10–12].

Two seminal studies on SE treatment were performed and published during our study period. The Rapid Anticonvulsant Medication Prior to Arrival Trial (RAMPART) was published in 2012 and showed the superiority of IM midazolam over lorazepam in prehospital treatment. The Established Status Epilepticus Treatment Trial (ESETT) was published in 2019 and showed that levetiracetam, fosphenytoin, and valproate were equally suitable for second-line therapy with convulsive SE [13, 19].

The aim of this study was to determine how recent SE treatment patterns have evolved over the last ten years (2012–2021) and to examine any associated changes in outcomes and mortality.

2 Patients and Methods

2.1 Study Settings and Design

This study analyzed the medical records of patients with SE treated at Frankfurt University Hospital during the 10-year trial period from January 2012 to December 2021. Frankfurt University Hospital offers comprehensive neurological care with particular expertise in epileptology and intensive care medicine. Its catchment area is primarily the city of Frankfurt and its surrounding area, comprising > 1,000,000 people (the population of Frankfurt was 764,474 on June 30, 2022; http://www.frankfurt.de).

We included both children and adults diagnosed with SE. Patients with insufficient data or initial treatment in another hospital for > 24 h were excluded. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines were followed [24]. This study was approved by the local ethics committee.

2.2 Status Epilepticus Definition

We defined tonic-clonic seizures as SE when they persisted for ≥ 5 min. Focal seizures with loss of consciousness or absences were also considered SE if they lasted ≥ 10 min [25]. Commonly, an SE is considered refractory (RSE) when first- and second-line therapies fail. This study defined RSE as a seizure failing to terminate despite administering two adequate ASMs (including a benzodiazepine). We considered seizures not terminating with anesthetic treatment ≥ 24 h as super-refractory (SRSE) [26, 27].

Status epilepticus was defined as terminated when seizure symptoms resolved and the patient returned to baseline or, in uncertain cases, when an electroencephalogram (EEG) no longer showed signs of SE. The EEGs were examined by certified neurologists and neuro-pediatricians (AS, FR, SSB, and MK). The Salzburg EEG criteria were used to diagnose nonconvulsive SE [28, 29].

We used the current definitions of the International League Against Epilepsy to define SE and categorize epilepsy type, seizure type, and epilepsy syndromes [25, 30–32]. All inpatient admissions diagnosed with International Statistical Classification of Diseases, Tenth Revision (ICD-10) codes for epilepsy (G40), SE (G41), and febrile convulsions (R56) were retrieved and checked to determine whether a SE occurred in those patients to ensure all SE cases were detected.

2.3 Data Acquisition and Outcome Parameters

Data on SE treatment were analyzed, including age, sex, refractoriness, previous epilepsy history, and modified Rankin Scale (mRS) score before admission and at discharge. An mRS of 3–5 was classified as a disability. Disabilities were recorded as already present at admission or newly acquired during treatment and persisting at discharge.

To examine medication patterns, we distinguished between prehospital and in-hospital therapy initiation and evaluated who provided the initial treatment (laypersons, medical personnel, or others). We collected the frequency of administration of each drug and dosage for the different SE therapy stages. We then analyzed the data by paired years.

For dosages, we recorded the first bolus given and the maximum dose given over 24 hours (maintenance dose) in milligrams. In addition, we calculated the dosage in milligrams per kilogram of body weight (mg/kg BW)

using the patient's weight. We used mRS and mortality at discharge and 30-day mortality to determine outcomes.

2.4 Literature Review on SE Treatment Patterns

We reviewed the literature from January 2010 to September 2022 in the PubMed and Cochrane Central Register of Controlled Trials databases to identify all relevant studies on SE treatment patterns. This search strategy combined the keywords "status epilepticus," "medication," "treatment," "outcome," "mortality," "benzodiazepines," "antiseizure medications," "anesthetics," and "narcotics." We checked the reference lists of the retrieved papers on SE medication to find additional potentially relevant studies.

2.5 Statistical Analysis

The data analysis was performed using IBM SPSS Statistics (version 28) and Bias (version 11.12) software. We defined three different cohorts: children (including adolescents; aged 0 to < 18 years at admission), adults (aged ≥ 18 years), and all patients. Univariable comparisons of proportions among these cohorts were performed using Pearson's chi-squared or Fisher's exact tests. Two-sided p values < 0.05 were considered statistically significant. We used the Bonferroni–Holm method to adjust p-values for multiple testing with a calculated p value < 0.001 considered statistically significant. We used the KAUST Biostatistics Research Group's freely available Robust Interrupted Time Series Toolbox (https://biostatistics-kaust.github.io/robust_time_series_toolbox/) to perform time-series analyses of the data. The statistically calculated change point was used to estimate the time of the change in each drug's use. The results of time series analyses were visualized using the GraphPad Prism (version 9) software.

3 Results

3.1 Patient Characteristics

We analyzed 1151 SE episodes in 1021 SE patients (mean age = 53.3 years, standard deviation [SD] = 28.3; median = 60.9; range: 0.1–99.8; 52.5 % [n = 533] female), of which 263 were in children (206 patients; mean age = 6.2 years; 39.3 % female) and 888 were in adults (815 patients; mean age = 65.1 years; 55.5 % female). Refractory SE was present in 521 (45.3 %) and SRSE in 116 (10.1 %) episodes. Prior epilepsy history was present in 48.9 % (n = 563). About half of all episodes (46 %) showed an mRS score of 3–5 at admission, indicating disability (Table 1).

3.2 Status Epilepticus Treatment with Benzodiazepines

Prehospital treatment with benzodiazepines was given in 32.8 % (n = 378) of episodes, by laypersons in 32.3 % (n = 122) and/or by the ambulance service in 76.7 % (n = 290) with varying application forms (IV, oral, buccal, intranasal, IM, or rectal). The percentage of episodes with prehospital treatment remained stable over time. In children, 53.6 % (n = 141) received prehospital treatment, compared to 26.7 % (n = 237) in adults (Fig. 1). Most children were treated by a layperson (63.1 % [n = 89]), while most adults were treated by the ambulance service (84.4 % [n = 200]).

In adults, midazolam was the most frequently given benzodiazepine prehospital throughout the entire study period, and its use showed an increasing trend over time (p = 0.72). The use of the other benzodiazepines was already below midazolam by 2012–2013. Diazepam and lorazepam use declined significantly over time (p < 0.001); clonazepam showed a decreasing trend (p = 0.01 Fig. 2). The prehospital benzodiazepine treatment pattern also showed a change over time in children. In 2012–2013, diazepam was used more frequently (75.6 % [n = 31]) than midazolam (29.3 % [n = 12]). In contrast, in 2020–2021, diazepam use had decreased significantly (p < 0.001) and was given in only 50.0 % (n = 11) of episodes compared to 81.8 % for midazolam (n = 18; p = 0.78). In children, lorazepam (2012–2013: 9.8 % [n = 4]; 2020–2021: 0 % [n = 0], p = 0.030) and clonazepam (2012–2013: 2.4 % [n = 1]; 2020–2021: 0 % [n = 0]; p = 0.42) use remained low.

In 2012–2013, lorazepam had the highest in-hospital administration rate (78.5 % of all episodes treated with benzodiazepines [n = 73]), followed by diazepam (11.8 % [n = 11]), midazolam (10.8 % [n = 10]), and clonazepam (8.6 % [n = 8]). Ten years later, midazolam use had increased significantly (66.5 % [n = 107]; p < 0.001) and was the most used benzodiazepine, while lorazepam use had decreased significantly (41.0 % [n = 66]; p = 0.003). We found these medication trends in children and adults (Fig. 2), although midazolam use did not significantly increase in children (p = 0.270). In-hospital clonazepam use showed a declining trend in children (2012–2013: 35.0 % [n = 7]; 2020–2021: 6.3 % [n = 1], p = 0.010) but a significant increase in adults (2012–2013: 1.4 % [n = 1]; 2020–2021: 19.3 % [n = 28], p < 0.001).

In adults, lorazepam was given at a mean dosage of 0.025 mg/kg BW, midazolam at 0.08 mg/kg BW, diazepam at 0.13 mg/kg BW, and clonazepam at 0.015 mg/kg BW. In children, lorazepam was given at a mean dosage of 0.06 mg/kg BW, midazolam at 0.24 mg/kg BW, diazepam at 0.015 mg/kg BW, and clonazepam at 0.04 mg/kg BW,

Table 1 Patient characteristics in the study cohort

Admission year	Number of episodes (patients)	Age, y (mean ± SD)	Age, y (median)	Age, y (range)	Female, %	RSE, % (No.[a])	SRSE, % (No.[b])	Mortality at discharge, % (No.[c])	30-day mortality, % (No.[c])	Prior epilepsy history, % (No.[d])	Acute symptomatic etiology, % (No.[e])	mRS of 3–5 at admission, % (No.)	mRS of 3–5 at discharge, % (No.)
All admissions (2012–2021)	1151 (1021)	53.3 ± 28.3	60.9	0.1–99.8	52.5	55.3 % (637)	10.1 % (116)	16.5 % (190)	18.9 % (217)	48.9 % (563)	32.3 % (372)	46.0 % (530)	53.1 % (611)
2012–2013	179 (150)	45.3 ± 31.5	54.7	0.1–93.3	50.7	56.4 % (101)	10.1 % (18)	15.1 % (27)	17.3 % (31)	59.2 % (106)	35.8 % (64)	51.4 % (92)	50.3 % (90)
2014–2015	233 (210)	54.6 ± 26.6	61.6	0.3–94.8	53.3	59.7 % (139)	11.6 % (27)	15.9 % (37)	16.3 % (38)	54.9 % (128)	29.6 % (69)	54.1 % (126)	57.5 % (134)
2016–2017	283 (246)	56.8 ± 25.5	63.0	0.6–99.8	48.0	41.0 % (116)	8.8 % (25)	14.1 % (40)	17.0 % (48)	46.6 % (132)	33.6 % (95)	40.3 % (114)	54.1 % (153)
2018–2019	213 (194)	51.1 ± 30.2	60.2	0.1–97.4	56.2	59.6 % (127)	5.6 % (12)	20.7 % (44)	22.1 % (47)	42.3 % (90)	31.9 % (68)	34.7 % (74)	48.8 % (104)
2020–2021	243 (221)	55.2 ± 28.2	60.6	0.1–96.5	53.4	63.4 % (154)	14.0 % (34)	17.3 % (42)	21.8 % (53)	44.0 % (107)	31.3 % (76)	51.0 % (124)	53.5 % (130)

No. number, *RSE* refractory SE, *SD* standard deviation, *SE* status epilepticus, *SRSE* super-refractory SE

[a]No. of episodes with RSE

[b]No. of episodes with SRSE

[c]No. of deaths

[d]No. of episodes with previous epilepsy

[e]No. of episodes with acute symptomatic etiology

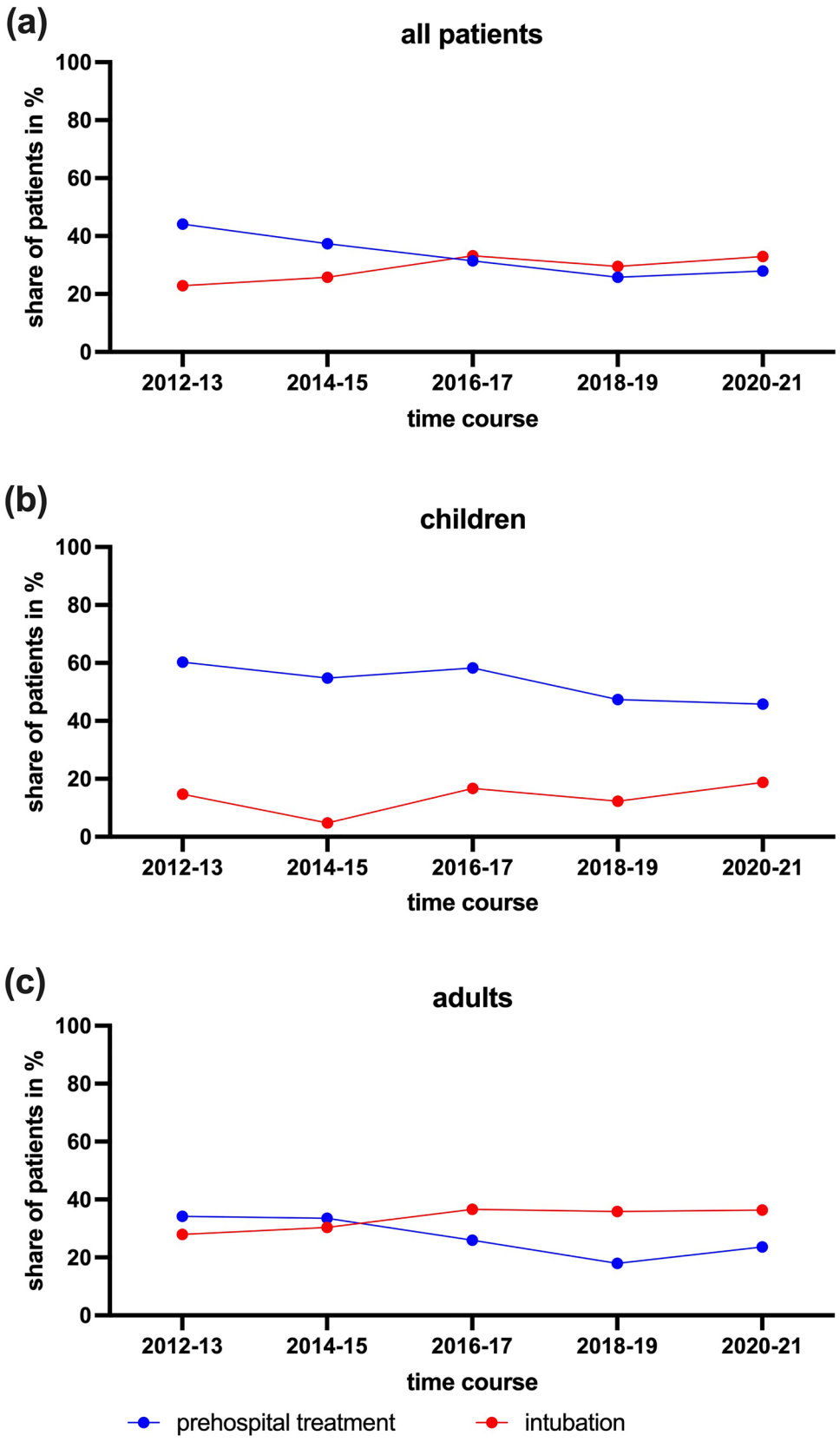

Fig. 1 Prehospital treatment and overall intubations in **a** all patients, **b** children, and **c** adults

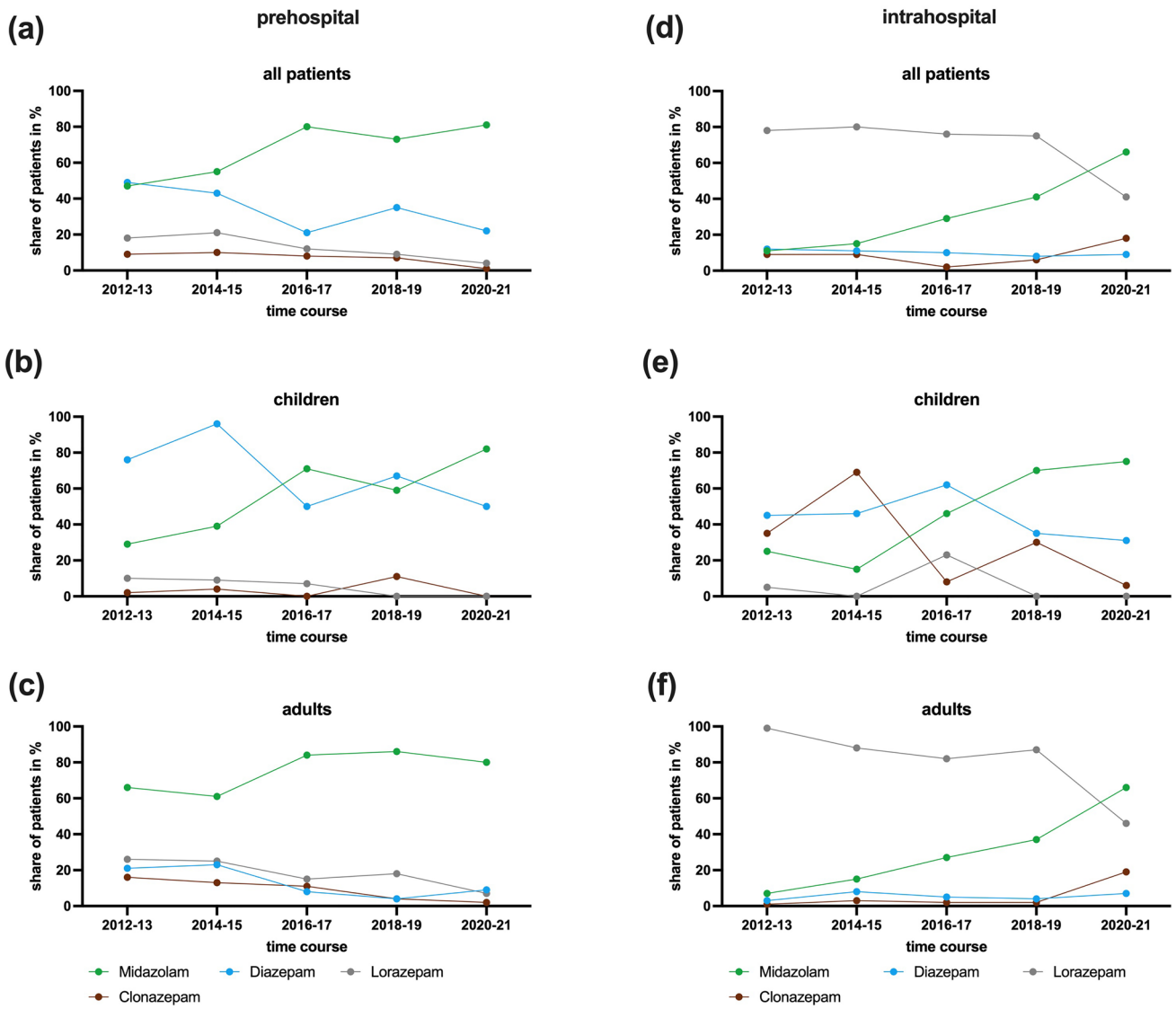

Fig. 2 Percentage of **a**, **d** all, **b**, **e** pediatric, and **c**, **f** adult episodes treated (**a**–**c**) prehospital and (**d**–**f**) in-hospital with benzodiazepines

details regarding median and mean bolus dosage are available in table (Online Resource 1).

Overall, benzodiazepines were given in 79.6 % of all SE episodes, showing an increasing trend during the study period from 76.5 % in 2012–2013 to 86.8 % in 2020–2021.

3.3 Status Epilepticus Treatment with ASMs

In-hospital, phenytoin and valproate use decreased significantly ($p < 0.001$), and phenobarbital showed a decreasing trend ($p = 0.02$), while the use of newer ASMs such as levetiracetam and lacosamide increased significantly ($p < 0.001$; Fig. 3). In 2012–2013, 62.4 % ($n = 88$) of episodes receiving second-line therapy were treated with levetiracetam and 27.0 % ($n = 38$) with lacosamide. In contrast, in 2020–2021, 84.7 % ($n = 171$) received levetiracetam and 63.4 % ($n = 128$) lacosamide. Brivaracetam was approved in Germany in 2016 and subsequently used in our hospital to treat 83 SE episodes.

In contrast to increasing newer ASM use in 2020–2021, only 26.2 % ($n = 53$) of ASM-treated episodes were given valproate (2012–2013: 59.6 % [$n = 84$]), 4.0 % ($n = 8$) phenytoin (2012–2013: 25.5 % [$n = 36$]), and 6.4 % ($n = 13$) phenobarbital (2012–2013: 14.9 % [$n = 21$]).

In children, phenobarbital was the most used ASM in 2012–2013 (56.8 % [$n = 21$]), followed by phenytoin (29.7 % [$n = 11$]). Since phenobarbital usage halved over time (2020–2021: 28.0 % [$n = 7$]), and phenytoin was not used in 2020–2021, both drugs showed a significant decrease in

children ($p < 0.001$). The mean phenytoin dosage was 8.8 mg/kg BW, and phenobarbital dosage was 6.8 mg/kg BW.

Levetiracetam replaced older ASMs in pediatric care (2018–2019) later than in adults (2014–2015). In children, the mean levetiracetam dosage was 22.5 mg/kg BW, it increased from 22.5 mg/kg BW (median = 20.5 mg/kg BW; mean = 409.8 mg, median = 350.0 mg) in 2012–2013 to 24.4 mg/kg BW (median = 22.0 mg/kg BW; mean = 480.4 mg, median = 400 mg) in 2020–2021. Maintenance levetiracetam dosages tended to increase in children from 2012–2013 (mean = 40.6 mg/kg BW, median = 40.0 mg/kg BW) to 2020–2021 (mean = 45.5 mg/kg BW, median = 47.4 mg/kg BW). In children, lacosamide showed an increasing trend from 2.7 % ($n = 1$) in 2012–2013 to 28.0 % ($n = 7$) in 2020–2021 ($p = 0.150$), with a mean dosage of 7.4 mg/kg BW. Valproate was given in 9.5 % ($n = 15$) of episodes in children with a mean dosage of 22.2 mg/kg BW. Brivaracetam has been given in two episodes in children since 2018.

In adults, levetiracetam (78.8 % [$n = 82$]) and valproate (79.8 % [$n = 83$]) had similarly high prescription levels in 2012–2013. However, valproate use decreased significantly to 27.7 % ($n = 49$, $p < 0.001$) by 2020–2021, while levetiracetam use increased significantly to 85.9 % ($n = 152$, $p < 0.001$). The mean levetiracetam dosage was 21.0 mg/kg BW. There was a trend toward higher bolus levetiracetam doses in adults over time, with the median bolus dose 18.1 mg/kg BW (median = 15.4 mg/kg BW; bolus: mean = 3211.5 mg, median = 3000.0 mg) in 2012–2013 but 23.3 mg/kg BW (median = 23.1 mg/kg BW; bolus: mean = 3695.7 mg, median = 4000.0 mg) in 2020–2021. Maintenance levetiracetam dosages remained constant in adults between 2012–2013 (mean = 49.4 mg/kg BW, median = 48.8 mg/kg BW) and 2020–2021 (mean = 51.0 mg/kg BW, median = 50.0 mg/kg BW). The mean valproate dosage was 13.99 mg/kg BW. The mean lacosamide bolus dosage was 2.6 mg/kg BW, details regarding median and mean bolus and maintenance dosage are available in table (Online Resource 1).

3.4 Status Epilepticus Treatment with Anesthetics

Intubations were performed more frequently over time in children and adults. Overall, 22.9 % ($n = 41$) of all episodes required intubation in 2012–2013 compared to 32.9 % ($n = 80$) in 2020–2021. However, children with SE were intubated less frequently than adults (Fig. 1). The medication pattern for anesthetic drugs in our SE cohort did not change appreciably over time (Fig. 4).

Continuous midazolam infusion and propofol remained the most frequently used third-line therapy drugs, although propofol use tended to decline ($p = 0.490$) while midazolam use tended to increase ($p = 0.39$). Therefore, 90.0 % ($n = 27$) of SE episodes treated with anesthetics were treated with propofol and 66.7 % ($n = 20$) with continuous midazolam infusion in 2012–2013, but only 67.4 % ($n = 31$) were treated with propofol and 73.9 % ($n = 34$) with continuous midazolam infusion in 2020–2021. Thiopental use decreased since it was given as third-line therapy to 20.0 % ($n = 6$) of episodes in 2012–2013 but no episodes in 2020–2021 ($p = 0.004$). However, ketamine use increased significantly from 6.7 % ($n = 2$) in 2012–2013 to 28.3 % ($n = 13$) in 2020–2021 ($p = 0.02$). Children were rarely treated with ketamine ($n = 2$) or thiopental ($n = 1$).

3.5 Outcome and Mortality

Disability at discharge did not differ over time, with 50.3 % of patients discharged with an mRS score of 3–5 in 2012–2013 compared to 53.5 % in 2020–2021, while disability before SE remained stable (51.4 % in 2012–2013 and 51.0 % in 2020–2021). We recorded a fatal outcome for 16.5 % of all SE episodes, with a 30-day mortality of 18.9 %. Mortality remained constant throughout the study period. At discharge, mortality was 15.1 % in 2012–2013 and 17.3 % in 2020–2021. The 30-day mortality was 17.3 % in 2012–2013 and 21.8 % in 2020–2021. Mortality in children was low at 1.9 % (remained constant during the study period at 1.5 % in 2012–2013 and 2.1 % in 2020–2021) as compared to the higher mortality rate in adults at 20.8 % (23.4 % in 2012–2013 and 21.0 % in 2020–2021). Disability at discharge decreased in children during the study period: 38.2 % had an mRS score of 3–5 in 2012–2013 compared to 31.3 % in 2020–2021. However, mRS scores before SE also decreased simultaneously in children: 36.8 % had an mRS score of 3–5 in 2012–2013 compared to 31.3 % in 2020–2021.

4 Discussion

In this large study of 1021 patients, midazolam emerged as the preferred benzodiazepine for SE treatment in both children and adults, both pre- and in-hospital. The same applies to the increased use of levetiracetam and lacosamide in children and adults, while the overall use of phenobarbital, phenytoin, and valproate use decreased. Mortality and outcome remain stable despite changes in medication patterns.

Different studies have analyzed SE treatment but not its trends over time [8, 33–42]. Only two previous studies evaluated medication trends but focused mainly on ASMs. However, our data are more recent since the other two studies only included patients up to 2012 and 2016 [43–45].

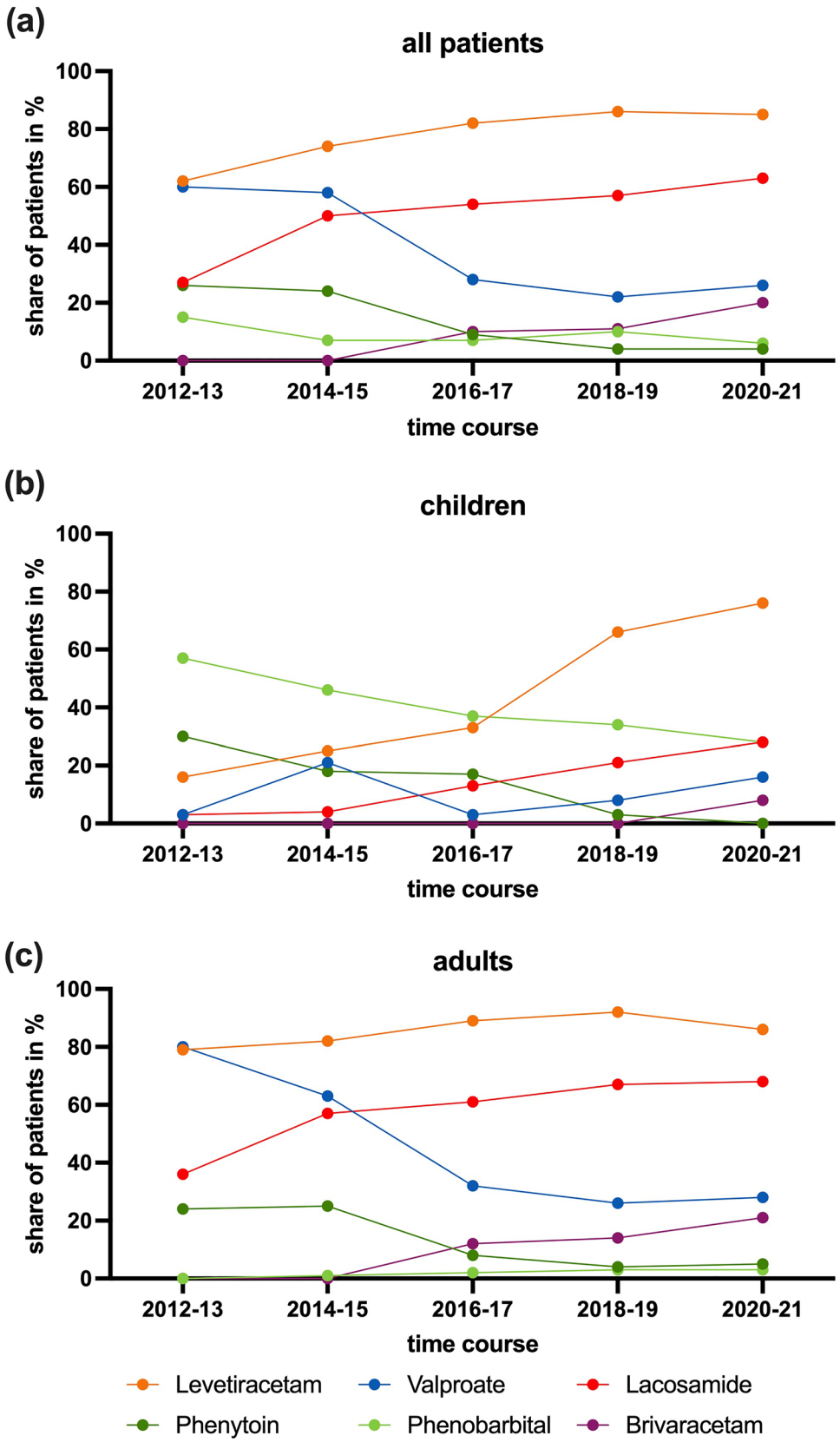

Fig. 3 Percentage of **a** all, **b** pediatric, and **c** adult episodes treated with ASMs

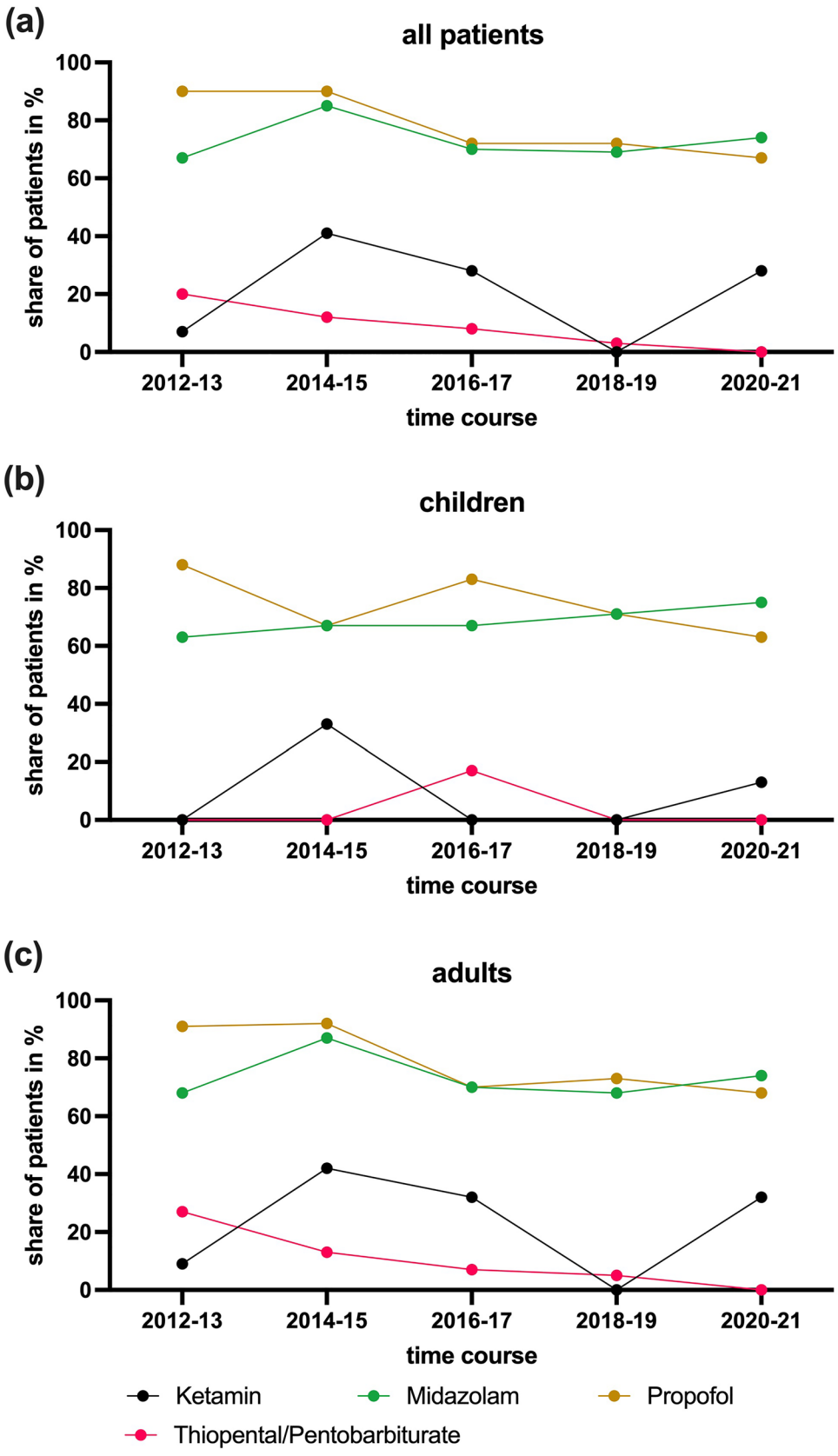

Fig. 4 Percentage of **a** all, **b** pediatric, and **c** adult episodes treated with anesthetics

This is the first study to examine the impact of the RAMPART and ESETT trials on medication patterns in SE. Another notable feature of this study is that it includes children and adults and analyzes them together and separately to identify treatment differences and similarities between them.

Status epilepticus must be treated promptly, ideally in the prehospital setting, since outcomes worsen when seizure control is not achieved within 1–2 hours after SE onset [6, 46, 47]. Overall, half of SE episodes in children and one-third of SE episodes in adults were treated prehospital in this study. However, we did not differentiate between SE episodes that started prehospital and those that occurred only during an in-hospital stay. Children treated prehospital were much more likely to be treated by a layperson than adults. This difference might reflect parents administering benzodiazepines to their children with known epilepsy during SE. In adults, a lack of a partner or caregiver has been shown to decrease rescue medication use [48], and adults presented with new-onset SE more frequently than children.

In this study, we aimed to investigate whether treatment patterns for first-line therapy changed during the study period. The publication of different studies favoring midazolam use during our study may have impacted the benzodiazepine medication behavior it found [13, 49, 50]. Notably, the RAMPART study was published in 2012, reporting numeric superiority and statistic noninferiority in efficacy and safety of IM midazolam over IV lorazepam in the prehospital setting for first-line SE medication [13]. A secondary analysis of the pediatric patients in the RAMPART study showed that the overall cohort's results also apply to them [15]. A meta-analysis from 2010 found midazolam to be superior to diazepam in any application mode and non-parenteral administration of midazolam to be as effective as parenteral administration of diazepam in pediatric SE therapy [49].

Our results show an increase in midazolam use in pre- and in-hospital first-line treatment for adults and children. Shortly after the RAMPART study was published and after the approval of buccal midazolam in the European Union (EU) in 2011 [51], midazolam became the preferred benzodiazepine in the prehospital setting for the overall cohort in 2014–2015. Midazolam was already the most frequently used prehospital benzodiazepine in adults when this study commenced. Nevertheless, there was a trend to use it even more frequently by the end of the study. In addition, there was a trend of increasing prehospital midazolam usage in children.

A more pronounced increase in in-hospital midazolam prescription was seen during the study period. Midazolam replaced lorazepam in adults and diazepam in children as the most frequently used benzodiazepine. Our results show a significant increase in midazolam use as first-line therapy in in-hospital therapy in the overall cohort and adults and trends of increasing usage in in-hospital pediatric therapy and prehospital treatment across all age groups. Several factors may have contributed to the increase in midazolam use. First, different publications have highlighted the efficacy and safety of midazolam. Second, the training of paramedic staff in our region is based on the algorithms for emergency care in the German state of Hesse. These exclusively recommend midazolam (IM or IV) for paramedics as first-line therapy [52]. Third, midazolam administration by parents has presumably become more common after the approval of buccal midazolam in the EU since this application route might be perceived as more socially compatible than other possible application types for laypersons. While in-hospital treatment was performed at different departments in our university hospital (e.g., neurology, pediatrics, and the emergency department) that comprise many treating clinicians, its internal guidelines recommend using buccal or intranasal midazolam until an IV access becomes available [53].

While this study was single-centered, and it could be argued that a general statement on changed medication behavior cannot be made based upon it, it included the medicating behavior of many physicians. For example, prehospital therapy is performed by various emergency physicians and paramedics not employed by Frankfurt University Hospital. In-hospital treatment was performed at different departments in our hospital such as neurology, pediatrics, and the emergency department that include many healthcare providers.

We found a general decline in traditional ASM use and an increase in newer ASM use, consistent with previous studies on medication use in SE [33–36, 41, 43, 44, 54]. Phenytoin has for many years been frequently used for second-line therapy in patients with SE. However, the ESETT randomized trial published in 2019 reported no difference in efficacy and safety between fosphenytoin, levetiracetam, and valproate. Therefore, any of these three drugs may be used for second-line SE treatment. Nevertheless, levetiracetam had the highest posterior probability of being the most effective in that trial [19]. A review of recent studies concluded that levetiracetam causes less frequent and often less severe side effects than phenytoin while being equally efficient [55]. Moreover, a Pakistani randomized controlled trial reported that levetiracetam might be more efficient than phenytoin in treating convulsive SE in children [56]. In this study, phenytoin had already disappeared from the top three most frequently used ASMs by 2012–2013, and its use continued to decline over time.

Most studies on SE medication report levetiracetam as the most frequent ASM used, consistent with the findings of the ESETT trial and our results [19, 33–37, 43, 54, 57]. Only one recent study from Norway published in 2018

showed that phenytoin remained the leading ASM, with levetiracetam only the fourth most used [39]. Their study period was 2001–2017, and evidence for levetiracetam being equally safe and effective as phenytoin was just emerging [58, 59].

In adults, we showed a consistently high prescription rate for levetiracetam, contrasting with the results of a study from Switzerland published in 2017, that found levetiracetam use still rising steadily [43, 45]. This difference can be explained by levetiracetam only being approved in Switzerland in 2008, during the study period of the Swiss study. In contrast, our study only started in 2012. Additionally, levetiracetam was already approved in Germany in 1999, and an IV solution became available in 2006 [60]. Therefore, its use might have already been established before our study [6].

The Swiss study also reported stable valproate use, while our results show a significant decline in valproate use in the overall cohort and adults [43, 45]. Valproate use declined in our cohort since it should be avoided in women of reproductive age due to its teratogenicity [61]. We cannot confirm the findings of the Swiss study, where the reported use of newer ASMs was accompanied by an increase in patients discharged with a disability (i.e., an mRS score of 3–5) [43, 45]. In this study, the proportion of episodes with an mRS score of 3–5 at discharge remained constant over the study period. Mortality did not change significantly throughout the study period, with an average of 16.5 % of episodes being fatal at discharge, consistent with previous cohort studies on SE [9, 33–37, 43–45]. In addition, the mortality at 30 days after discharge (17.3 % in 2012–2013 and 21.8 % in 2020–2021) remained relatively stable over time. However, patients treated in 2020–2021 (mean = 55.2 ± 28.2 years, median = 60.6, range = 0.1–96.5) were older than those in 2012–2013 (mean = 45.3 ± 31.5, median = 54.7, range = 0.1–93.3), which may have negatively impacted survival.

Several studies on SE treatment [8, 62–64] and comparisons with the dosage recommended by the German SE guidelines for adults indicate that both ASMs and benzodiazepines were usually underdosed in bolus administration, which is consistent with our adult cohort. In contrast, most benzodiazepines were correctly dosed in our pediatric cohort. However, dosing in children is usually higher than in adults, likely attributable to the lower body weight of children. Second-line bolus therapy was generally underdosed for all ASMs in adults and children, except for lacosamide. However, no recommendations for maintenance doses exist in current SE guidelines [10].

Notably, ASM maintenance doses in adults generally align with the guideline recommendations for bolus administration in SE [10]. Therefore, we anticipate that an ASM bolus is usually initially underdosed. However, when it does not terminate the SE, a maintenance dose consistent with the guideline's recommendations for bolus dosage is achieved during therapy.

Notably, while the German SE guidelines do not provide recommendations specifically for children, some international guidelines do include them. The recommended benzodiazepine dosages from several international agencies [11, 12, 65–71] and the German SE guidelines [10] are summarized separately for adults and children in Table 2. There are recommended ranges for lorazepam (0.05–0.1 mg/kg BW), midazolam (0.1–0.2 mg/kg BW), diazepam (0.15–0.5 mg/kg BW), and clonazepam (0.01–0.05 mg/kg BW). Based on these ranges, our average doses are all within those recommended, except for midazolam. However, midazolam is often not administered IV, and Table 2 refers only to IV administration. It should be noted that this study evaluated the dosages for lorazepam (three episodes) and clonazepam (eight episodes) in only a few cases in children.

Propofol was the most frequently used drug for third-line therapy, only prescribed slightly more often than continuous midazolam infusion since both drugs were usually given together. Our results are consistent with those of other SE treatment studies, most of which found propofol to be given most often [33, 37, 39], with only one study describing continuous midazolam infusion as the most used [36]. However, this study included only a small number of third-line therapy cases, especially in the pediatric cohort (196 adult episodes and 32 pediatric episodes).

This study had certain limitations. First, it was single-centered and conducted at Frankfurt University Hospital, which primarily has an urban catchment area that does not represent the entire German population. Second, we investigated diverse patients of all ages with various SE severities, comorbidities, etiologies, and semiologies. Therefore, individual patients may have already had differing prognoses before treatment. Third, the German SE guidelines and treatment recommendations were updated during our study period (in 2020), which might have influenced the medication or dosing trends we identified. Fourth, the study's retrospective design made us reliant on the completeness and accuracy of medical records from different departments. Therefore, documentation errors are possible, and under-ascertainment of cases cannot be ruled out.

5 Conclusions

We observed continual changes in SE medication within the first two therapy stages. After the RAMPART trial was published in 2012, there was an apparent trend toward initial

Table 2 Benzodiazepine dosages in international guidelines [10–12, 65–71]

	Guideline	Year of publication	Midazolam		Diazepam		Lorazepam		Clonazepam	
			Bolus	Maximum dose	Bolus	Maximum dose	Bolus	Maximum dose	Bolus	Maximum dose
Adults	SIGN	2015 (revised 2018)	NR	NR	10 mg	NR	4 mg	NR	NR	NR
	American Epilepsy Society	2016	NR	NR	0.15–0.20 mg/kg	10 mg	0.1 mg/kg	4 mg	NR	NR
	German AWMF guideline	2020	0.2 mg/kg	10 mg	0.15–0.20 mg/kg	10 mg	0.1 mg/kg	4 mg	0.015 mg/kg	1 mg
	Guidelines for the Evaluation and Management of SE (USA)	2012	NR	NR	0.15 mg/kg	10 mg	0.1 mg/kg	4 mg	NR	NR
	Hong Kong Epilepsy Society	2017	NR	NR	0.15–0.20 mg/kg	10 mg	0.1 mg/kg	4 mg	NR	NR
	Vademecum antiepilepticum	2021	5–10 mg	NR	10–30 mg	NR	4 mg	8 mg	1–3 mg	NR
Children	American Epilepsy Society	2016	NR	NR	0.15–0.20 mg/kg	10 mg	0.1 mg/kg	4 mg	NR	NR
	Canadian Paediatric Society	2021	0.1 mg/kg	5 mg	0.30 mg/kg	5–10 mg	0.1 mg/kg	4 mg	NR	NR
	Emergency Medical Services for Children (USA)	2022	0.1 mg/kg	10 mg	NR	NR	0.1 mg/kg	4 mg	NR	NR
	Guidelines for the Evaluation and Management of SE (USA)	2012	NR	NR	0.2–0.5 mg/kg	NR	0.1 mg/kg	4 mg	NR	NR
	UpToDate	2021	NR	NR	0.2 mg/kg	10 mg	0.1 mg/kg	4 mg	NR	NR
	Vademecum antiepilepticum	2021	0.15 mg/kg	NR	0.15–0.30 mg/kg	NR	0.05–0.10 mg/kg	NR	0.01–0.05 mg/kg	NR
	Vasquez et al.	2020	0.2 mg/kg	10 mg	0.15 mg/kg	10–20 mg	0.1 mg/kg	4 mg	NR	NR

AWMF Association of the Scientific Medical Societies in Germany, *NR* not reported, *SE* status epilepticus, *SIGN* Scottish Intercollegiate Guidelines Network

midazolam therapy in all age groups, both prehospital and in-hospital. Newer ASMs, such as levetiracetam and lacosamide, are replacing older ASMs, such as phenytoin and valproate, in second-line therapy since they have fewer reported side effects. Despite these changes, mortality and disability after suffering SE have remained stable. Further studies are needed to determine whether these trends will persist in the long term and whether they affect outcomes such as quality of life and long-term mortality.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s40263-023-01049-w.

Acknowledgements We thank all colleagues and staff at the study center for their support in conducting this study.

Funding Open Access funding enabled and organized by Projekt DEAL.

Declarations

Funding There is no funding to report.

Conflicts of interest L. Purwien, L.M. Willems, M. Merker, and M. Czabanka do not report competing interests. S. Schubert-Bast reports personal fees from Eisai, Desitin Pharma, GW Pharmaceuticals, Ethypharm, UCB, and Zogenix. M. Kieslich reports personal fees from Desitin Pharma and Eisai GmbH. F. Rosenow reports personal fees from Angelini Pharma, Arvelle Therapeutics, Desitin Arzneimittel, Eisai GmbH, GW Pharmaceuticals, Jazz Pharmaceuticals, Roche Pharma, and UCB and grants from the Detlev-Wrobel-Fonds for Epilepsy Research, the CHAJA-Foundation, the Deutsche Forschungsgemeinschaft, the LOEWE Programme of the State of Hesse, and the European Union. A. Strzelczyk reports personal fees and grants from Angelini Pharma (Arvelle), Biocodex, Desitin Arzneimittel, Eisai, Jazz (GW) Pharmaceuticals, Marinus Pharma, Precisis, Takeda, UCB Pharma (Zogenix), and UNEEG Medical. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or conflict with the subject matter or materials discussed in this manuscript apart from those disclosed.

Ethics approval This study was approved by the Ethics Advisory Board of Goethe University (Frankfurt am Main, Germany) before it was conducted (reference number 20-951).

Consent to participate Not applicable due to retrospective nature of the study.

Consent for publication All authors approved the final manuscript for submission.

Availability of data and material The datasets generated and/or analyzed during this study are available from the corresponding author upon reasonable request.

Code availability Not applicable.

Author contributions A. Strzelczyk conceived the idea for the study, was responsible for the data collection, and developed the idea for the analysis. L. Purwien, S. Schubert-Bast, and A. Strzelczyk collected the data. A. Strzelczyk, L.M. Willems, and L. Purwien processed the data and performed the statistical analyses. L.M. Willems created the figures. L. Purwien and A. Strzelczyk drafted the initial manuscript. All authors wrote, edited, and significantly contributed to the final manuscript.

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Authors and Affiliations

Leonore Purwien[1,2] · Susanne Schubert-Bast[1,2,3] · Matthias Kieslich[1,2,3] · Michael W. Ronellenfitsch[2,4,5] · Michael Merker[3] · Marcus Czabanka[6] · Laurent M. Willems[1,2] · Felix Rosenow[1,2] · Adam Strzelczyk[1,2]

✉ Adam Strzelczyk
strzelczyk@med.uni-frankfurt.de

1 Epilepsy Center Frankfurt Rhine-Main and Department of Neurology, Center of Neurology and Neurosurgery, Goethe-University and University Hospital Frankfurt, Schleusenweg 2-16 (Haus 95), 60528 Frankfurt am Main, Germany

2 LOEWE Center for Personalized Translational Epilepsy Research (CePTER), Goethe-University Frankfurt, Frankfurt am Main, Germany

3 Department of Child and Adolescent Medicine, Neuropediatrics, Goethe-University and University Hospital Frankfurt, Frankfurt am Main, Germany

4 Dr. Senckenberg Institute of Neuro-oncology, Goethe-University Frankfurt, Frankfurt am Main, Germany

5 Frankfurt Cancer Institute (FCI), Goethe-University Frankfurt, Frankfurt am Main, Germany

6 Department of Neurosurgery, Goethe-University and University Hospital Frankfurt, Frankfurt am Main, Germany