Epilepsia®

FULL-LENGTH ORIGINAL RESEARCH

Benzodiazepine administration patterns before escalation to second-line medications in pediatric refractory convulsive status epilepticus

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Abstract

Objective: This study was undertaken to evaluate benzodiazepine (BZD) administration patterns before transitioning to non-BZD antiseizure medication (ASM) in pediatric patients with refractory convulsive status epilepticus (rSE).

Methods: This retrospective multicenter study in the United States and Canada used prospectively collected observational data from children admitted with rSE between 2011 and 2020. Outcome variables were the number of BZDs given before the first non-BZD ASM, and the number of BZDs administered after 30 and 45 min from seizure onset and before escalating to non-BZD ASM.

Results: We included 293 patients with a median (interquartile range) age of 3.8 (1.3–9.3) years. Thirty-six percent received more than two BZDs before escalating, and the later the treatment initiation was after seizure onset, the less likely patients were to receive multiple BZD doses before transitioning (incidence rate ratio [IRR] = .998, 95% confidence interval [CI] = .997–.999 per minute, p = .01). Patients received BZDs beyond 30 and 45 min in 57.3% and 44.0% of cases, respectively. Patients with out-of-hospital seizure onset were more likely to receive more doses of BZDs beyond 30 min (IRR = 2.43, 95% CI = 1.73–3.46, p < .0001) and beyond 45 min (IRR = 3.75, 95% CI = 2.40–6.03, p < .0001) compared to patients with in-hospital seizure onset. Intermittent SE was a risk factor for more BZDs administered beyond 45 min compared to continuous SE (IRR = 1.44, 95% CI = 1.01–2.06, p = .04). Forty-seven percent of patients (n = 94) with out-of-hospital

onset did not receive treatment before hospital arrival. Among patients with out-of-hospital onset who received at least two BZDs before hospital arrival ($n = 54$), 48.1% received additional BZDs at hospital arrival.

Significance: Failure to escalate from BZDs to non-BZD ASMs occurs mainly in out-of-hospital rSE onset. Delays in the implementation of medical guidelines may be reduced by initiating treatment before hospital arrival and facilitating a transition to non-BZD ASMs after two BZD doses during handoffs between pre-hospital and in-hospital settings.

KEYWORDS

benzodiazepine, epilepsy, pediatric, seizure, status epilepticus, treatment

1 | INTRODUCTION

Status epilepticus (SE) affects 17–23/100,000 children per year,[1–4] with short-term mortality of 0%–3%[1,3,5–8] and frequent, related neurocognitive sequelae.[9] Refractory SE (rSE) ensues when SE does not respond to initial antiseizure medications (ASMs), and the outcome is often worse in rSE.[10]

Major prognostic factors for SE outcome are age, etiology, and time to treatment.[6,9,11,12] Among these factors, time to treatment, including treatment escalation, is most amenable to modification. There is no evidence-based timeline on when to administer each ASM, although animal models suggest that benzodiazepines (BZDs) may progressively become less efficacious after 30 min of ongoing seizure activity.[13,14] Current SE guidelines recommend administration of the first BZD within 5–10 min from seizure onset and a transition to non-BZD ASMs at 10–20 min from seizure onset.[15,16] However, in clinical practice, treatment often occurs more slowly than recommended by guidelines.[17,18] Slower treatment is independently associated with longer seizure duration, increased need for continuous infusions, more frequent hypotension, and increased mortality.[11,19] No studies have focused on BZD administration patterns before escalating to non-BZD ASMs in rSE.

We aimed to describe the escalation from BZDs to non-BZD ASMs in patients with rSE in clinical practice, and analyze potential risk factors related to deviations from treatment guideline recommendations at this initial stage. We hypothesized that patients received a higher number of BZD doses than recommended by guidelines before transitioning to non-BZD ASMs, with applications frequently outside the most efficacious timeframe.

Key Points

- We evaluated BZD administration patterns before transitioning to second-line medication in pediatric refractory convulsive status epilepticus
- More than one third of patients received more than two BZDs before escalating to a non-BZD ASM
- More than half of patients received BZD doses after 30 min from seizure onset
- Out-of-hospital seizure onset and intermittent SE were associated with the failure to escalate from BZDs to non-BZD ASMs
- In approximately half of patients who received two or more BZDs before hospital arrival, the rescue algorithm was restarted following patient handoffs

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2 | MATERIALS AND METHODS

2.1 | Standard protocol approvals, registrations, and patient consents

The study was approved by the institutional review board at each participating institution. Written informed consent was obtained from parents or guardians.

2.2 | Study design

We retrospectively analyzed data from a prospective, observational study at 19 pediatric hospitals in the United

States and Canada within the Pediatric Status Epilepticus Research Group (pSERG).[20] This multicenter study collects data prospectively on patients with rSE, with the overall goal of delineating strategies for improving the management and eventually the outcome of children with SE.[20] Data regarding time to treatment in the first 81 patients,[21] the influence of a prior diagnosis of epilepsy and of a prior episode of SE on time to treatment,[22] the association of delays to treatment with short-term outcomes,[11] and the factors associated with treatment delays[23] have been published previously. Information on the cumulative first-line BZD dosing within a range of 10 min after treatment initiation in patients who underwent rSE, different types of BZDs used, routes of administration, and the effect on outcome were presented in a different article.[24] However, the pattern of separate BZD dose administration from SE onset in the setting of the delayed transition to non-BZD ASM, irrespective of the cumulative BZD dosing within the first 10 min of treatment initiation, have not been analyzed.

2.3 | Patients

Inclusion criteria were (1) admission to a pSERG center between June 2011 and February 2020, (2) age from 1 month to 21 years, and (3) focal or generalized convulsive seizures at the onset that evolved into rSE. In our study, rSE was considered when seizures continued after administration of at least two different ASM types, including at least one BZD and one non-BZD ASM. Exclusion criteria were (1) nonconvulsive SE detected on electroencephalogram without convulsive seizures at onset or limited to infrequent myoclonic jerks; (2) no data on relevant variables such as age, sex, location of rSE onset, type of SE, convulsive duration, time to administration of the first BZD, dose of the first BZD, and time to administration of the first non-BZD ASM; and (3) unconventional transition strategies, including first non-BZD ASM received before or at the same time as first BZD, first continuous infusion received before or at the same time as first BZD, or first continuous infusion received before or at the same time as first non-BZD ASM.[15] An inclusion diagram is detailed in Figure S1 (https://github.com/tsheehan01/BZD_Transition). If a patient had more than one episode of rSE during the study period, only the first episode was included to meet the assumption of independence of observations.

Data were collected with a standardized data acquisition tool and were based on caregivers' interviews, care provider documentation in the medical records, and emergency medical services (EMS) documentation, if applicable. Subsequently, data were entered into an electronic database hosted by Cincinnati Children's Hospital

Medical Center. Details of the pSERG consortium are available in the original pSERG research plan.[20]

2.4 | Variables

The primary outcome variable was the number of BZD doses administered from the beginning of SE treatment and before escalating to the first non-BZD ASM. The variables analyzed in the multivariate model were age (continuous in years), sex, type of SE (intermittent, defined as multiple seizures without return to baseline; or continuous, considered a single prolonged seizure), location of SE onset (in hospital/out of hospital), prior epilepsy (yes/no), prior SE (yes/no), time to treatment initiation from seizure onset (continuous in minutes), and inadequate first BZD dosing (yes/no; first BZD dose was defined as inadequate if a patient received less than 100% of the minimum recommended dose based on current medical guidelines for the treatment of SE,[15,16] detailed in the methodology of Vasquez et al.[24]). We did not include the ASM as chronic medication as a variable in the model because it is highly correlated with the variable prior epilepsy.

The secondary outcome variables were (1) the number of BZD doses administered beyond 30 min from seizure onset and before non-BZD ASM, and (2) the number of BZD doses administered beyond 45 min from seizure onset and before non-BZD ASM. The variables analyzed in these multivariate models were age (continuous in years), sex, type of SE (intermittent/continuous), location of SE onset (in hospital/out of hospital), prior epilepsy (yes/no), and prior SE (yes/no). The threshold of 30 min onward after seizure onset was chosen because it aligns with the classical definition of SE[25] and because responsiveness to BZDs in animal models is markedly lower after that time point.[26–28] However, limited animal and human series with prolonged SE presented complete resolution after a single BZD dose, suggesting a potential involvement of other factors in BZD response besides seizure duration, or the need for longer seizure duration to develop BZD resistance in some cases.[29,30] As responsiveness to BZDs may still be present later, we added an additional threshold of 45 min.

2.5 | Statistical analysis

Demographic and clinical characteristics were summarized using descriptive statistics. We initially used multivariate negative binomial regression models in all cases, because its dispersion parameter allows unequal mean and variance. A large number for theta obtained when modeling the primary outcome with the negative binomial

regression and the likelihood ratio test supported the use of Poisson regression in this specific case. Unless stated otherwise, continuous variables are presented as median (interquartile range [IQR]) and categorical variables are presented as number (percentage). A conventional alpha level of .05 was considered statistically significant for all analyses. All statistical analyses were performed with R (v3.4.1),[31] RStudio,[32] and the packages gmodels,[33] gdata,[34] tableone,[35] dplyr,[36] survival,[37] ggplot2,[38] and MASS.[39]

2.6 | Data availability statement

All relevant data, statistical analyses, and results can be found in File S2 (https://github.com/tsheehan01/BZD_Transition).

3 | RESULTS

3.1 | Study population

We included 293 patients (55% males) with a median (IQR) age of 3.8 (1.3–9.3) years. rSE started out of hospital in 201 (69%) patients and in hospital in 92 (31%) patients. Table 1 summarizes the main demographic and clinical features. Among patients with out-of-hospital onset, the first BZD was administered by caregivers in 56 (27.9%) patients, EMS in 51 (25.4%) patients, a secondary hospital in 47 (23.4%) patients, and a referral hospital in 47 (23.4%) patients. Ninety-four (46.8%) patients with out-of-hospital onset did not receive any rescue medication until hospital arrival. Among 54 patients who received two or more BZDs in the prehospital setting by caregivers or EMS, 26 (48.1%) received at least one additional BZD at hospital arrival as the first in-hospital ASM.

3.2 | Primary outcome

The number of BZD doses administered from the beginning of SE treatment and before escalating to the first non-BZD ASM is depicted in Figure 1 (data table in File S3, https://github.com/tsheehan01/BZD_Transition). One hundred six (36.2%) patients received more than two BZDs before escalating to a non-BZD ASM; 111 (37.9%) patients received two BZDs before a non-BZD ASM. In the multivariate model, out-of-hospital SE onset presented a trend toward a higher number of BZDs compared to in-hospital SE onset (incidence rate ratio [IRR] = 1.17, 95% confidence interval [CI] = .99–1.40, $p = .06$). The later the treatment initiation was from seizure onset, the less likely a patient was to receive multiple doses of BZD before

escalating to a non-BZD ASM (IRR = .998, 95% CI = .997–.999 per min, $p = .01$). An underdosed first BZD did not affect the final number of BZDs administered before transitioning (IRR = 1.00, 95% CI = .85–1.17, $p = .99$). All statistical results are summarized in File S4 (https://github.com/tsheehan01/BZD_Transition).

3.3 | Secondary outcomes

The number of BZD doses administered beyond 30 and 45 min from seizure onset and before non-BZD ASM are shown in Figures 2 and 3, respectively (data tables in File S5, https://github.com/tsheehan01/BZD_Transition). The percentages of patients who received at least one BZD beyond 30 and 45 min were 57.3% and 44%, respectively. In the multivariate models, patients who presented with out-of-hospital SE onset were more likely to receive more doses of BZDs compared to in-hospital SE onset beyond 30 min (IRR = 2.43, 95% CI = 1.73–3.46, $p < .0001$) and 45 min (IRR = 3.75, 95% CI = 2.40–6.03, $p < .0001$). Also, patients who presented with intermittent SE were more likely to receive more doses of BZDs compared to continuous SE beyond 45 min (IRR = 1.44, 95% CI = 1.01–2.06, $p = .04$). We included an exploratory interaction term between SE location onset and SE type that was not statistically significant. All statistical results are summarized in File S4 (https://github.com/tsheehan01/BZD_Transition).

4 | DISCUSSION

In our study population of children with rSE, more than one third of patients received more than two BZDs before escalating to a non-BZD ASM, and more than half of patients received BZDs after 30 min from seizure onset. Remarkably, in about half of patients who received two or more BZDs before hospital arrival, the rescue algorithm was restarted in patient handoffs at the interface between prehospital and in-hospital settings. Early treatment initiation for SE—compared to delayed initiation—was associated with a higher likelihood of receiving additional BZD doses before transitioning, and out-of-hospital SE onset and intermittent SE were risk factors for receiving BZDs beyond 30 min after seizure onset. Although receiving an underdosed first BZD may hypothetically justify repeated BZD doses, our model, adjusted for potential confounders, showed that the final BZD count was not driven by this factor.

Time to treatment initiation may play a role in the final BZD count based on our multicenter data. If treatment for SE was started later from seizure onset, patients were less

TABLE 1 Demographic and clinical characteristics

Characteristic	Patients in the entire cohort, N = 293	Patients with out-of-hospital onset, n = 201	Patients with in-hospital onset, n = 92
Age at SE in years			
Median (IQR)	3.8 (1.3–9.3)	3.2 (1.2–8.9)	4.8 (2.0–10.2)
Sex, n (%)			
Male	162 (55.3%)	120 (59.7%)	42 (45.7%)
Female	131 (44.7%)	81 (40.3%)	50 (54.3%)
Race, n (%)			
White	187 (63.8%)	126 (62.7%)	61 (66.3%)
African American	57 (19.5%)	42 (20.9%)	15 (16.3%)
American Indian/Alaska Native	1 (.3%)	0 (0%)	1 (1.1%)
Asian	10 (3.4%)	5 (2.5%)	5 (5.4%)
Arabic	8 (2.7%)	5 (2.5%)	3 (3.3%)
Hawaiian/Pacific Islander	2 (.7%)	2 (1.0%)	0 (0%)
Unknown/not reported	28 (9.6%)	21 (10.4%)	7 (7.6%)
Ethnicity, n (%)			
Hispanic or Latino	43 (14.7%)	32 (15.9%)	11 (12.0%)
Not Hispanic or Latino	225 (76.8%)	150 (74.6%)	75 (81.5%)
Unknown/not reported	25 (8.5%)	19 (9.5%)	6 (6.5%)
Medical history, n (%)[a]			
DD/ID	154 (52.6%)	108 (53.7%)	46 (50.0%)
Cerebral palsy	31 (10.6%)	19 (9.5%)	12 (13.0%)
History of epilepsy	146 (49.8%)	102 (50.7%)	44 (47.8%)
History of SE	63 (21.5%)	40 (19.9%)	23 (25.0%)
No past neurological history	96 (32.8%)	60 (29.9%)	36 (39.1%)
Duration of convulsive SE, min			
Median (IQR)	127 (60–286)	140 (75–300)	108 (48–182)
Type of SE, n (%)			
Continuous	102 (34.8%)	75 (37.3%)	27 (29.3%)
Intermittent	191 (65.2%)	126 (62.7%)	65 (70.7%)
Etiology of SE, n (%)			
Unknown	104 (35.5%)	71 (35.3%)	33 (35.9%)
Structural	70 (23.9%)	44 (21.9%)	26 (28.3%)
Genetic	57 (19.5%)	44 (21.9%)	13 (14.1%)
Metabolic	15 (5.1%)	9 (4.5%)	6 (6.5%)
Other	47 (16.0%)	33 (16.4%)	14 (15.2%)
Time to first BZD from seizure onset, min			
Median (IQR)	15 (5–37)	20 (5–50)	8 (4–20)
Inadequate first BZD dosing, n (%)			
Yes	166 (56.7%)	106 (52.7%)	60 (65.2%)
No	127 (43.3%)	95 (47.3%)	32 (34.8%)
Time to first non-BZD ASM from seizure onset, min			
Median (IQR)	63 (35–126)	76 (45–155)	39 (24–72)

Abbreviations: ASM, antiseizure medication; BZD, benzodiazepine; DD, developmental delay; ID, intellectual disability; IQR, interquartile range (first quartile Q_1 to third quartile Q_3); SE, status epilepticus.

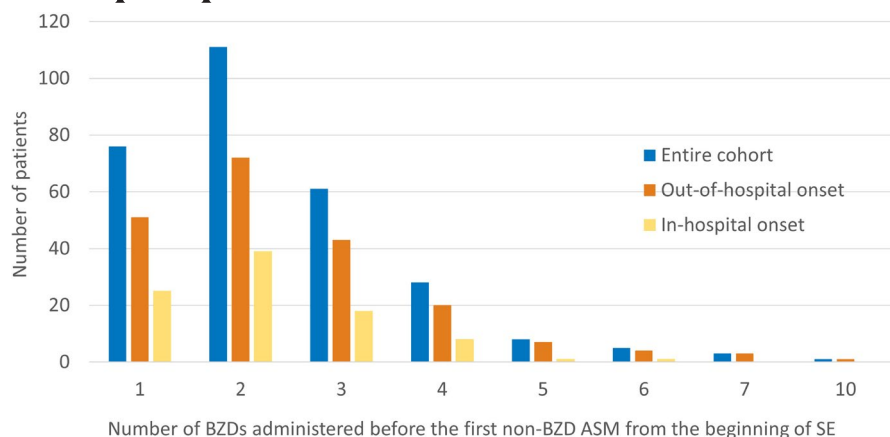[a]Percentages do not add up to 100% because patients may belong to more than one category.

likely to receive multiple doses of BZDs before transitioning to a non-BZD ASM. A potential explanation may be that with clear evidence of evolution into established SE, the care team more readily recognizes the need to escalate to second-line ASM and to avoid additional trials of BZDs. As there is no prior literature analyzing factors promoting multiple BZD dosing, we cannot compare our results with other studies.

The location of SE onset is related to the final BZD count based on our multicenter data. Out-of-hospital SE onset showed a trend toward a higher total number of BZD doses compared to in-hospital onset, and this difference was more prominent with a longer time from seizure onset. Potential explanations of this factor based on our data and prior literature[18] may be related to different series of events. First, a considerable proportion of patients with out-of-hospital SE onset are not receiving any BZD before hospital arrival, or some patients receive multiple doses of BZD because most EMS personnel are not authorized to give a second-line ASM and may not have other options available.[40–42] The prehospital setting is a key area for a timely and optimized management of SE, because most patients start seizing at this location; however, the lack of standardized EMS guidelines that are aligned with medical protocols, given the challenges and limitations of SE care in the field, hinder optimal prehospital care. Second, transportation to the hospital takes time.[43] Third, if the patient did not receive any BZD out of the hospital, the treatment starts late once the patient arrives at the hospital; conversely, if the treatment was started outside the hospital by caregivers or EMS, the medical team typically repeats a trial of BZD in the hospital setting, even if the patient had received two or more BZDs before hospital arrival.

The influence of nodes of care on breakdowns of treatment administration and escalation may play a role. Improved communication between each level of care, continuous documentation and charting that travel with the patient, and confidence in the treatment administered

by first responders (caregivers and EMS) or outside emergency departments in primary or secondary medical centers may prevent iterative treatments, thus making transitions between steps in the treatment algorithm smoother. Patient handoffs are a critical source of miscommunication and have the potential to lead to adverse events.[44,45] Specifically, a recent literature review raised concerns about clinical handovers at the interface between prehospital and in-hospital settings,[46] as sign-outs in emergency conditions, in noisy and stressful environments, in addition to a lack of time, may further complicate information transfer.[46]

Furthermore, SE treatment initiation is often delayed, and catch-up dosing does not consider timing. Many initial BZD doses and additional administration trials occur outside the most efficacious timeframe, whereas expediting or overlapping an escalation to non-BZD ASMs may increase the likelihood of SE cessation and ultimately reduce poor outcomes associated with this condition.[1,41,47,48] Although human studies on early polytherapy are still scarce, preclinical data support combining a BZD with a second-line ASM or an N-methyl-D-aspartate receptor antagonist to increase seizure control.[49]

Intermittent SE is related to more delayed treatment initiation or access to care[23,41] and may also promote new trials with BZDs later in time before escalating to non-BZD ASMs. A potential explanation may be uncertainty regarding response to BZD by the care provider or clinical difficulties in recognizing recurrent convulsive seizures as intermittent SE to pursue the next lines of ASM. Future research assessing the risk–benefit ratio of treating after a first seizure and subsequent drowsiness, as well as better biomarkers or technology in the field to help predict evolution into SE, may mitigate uncertainty and improve the management of this condition.

This study highlights a need for an optimized escalation to non-BZD ASMs after adequate administration of BZD doses, which is important because nonadherence to SE guidelines may negatively impact
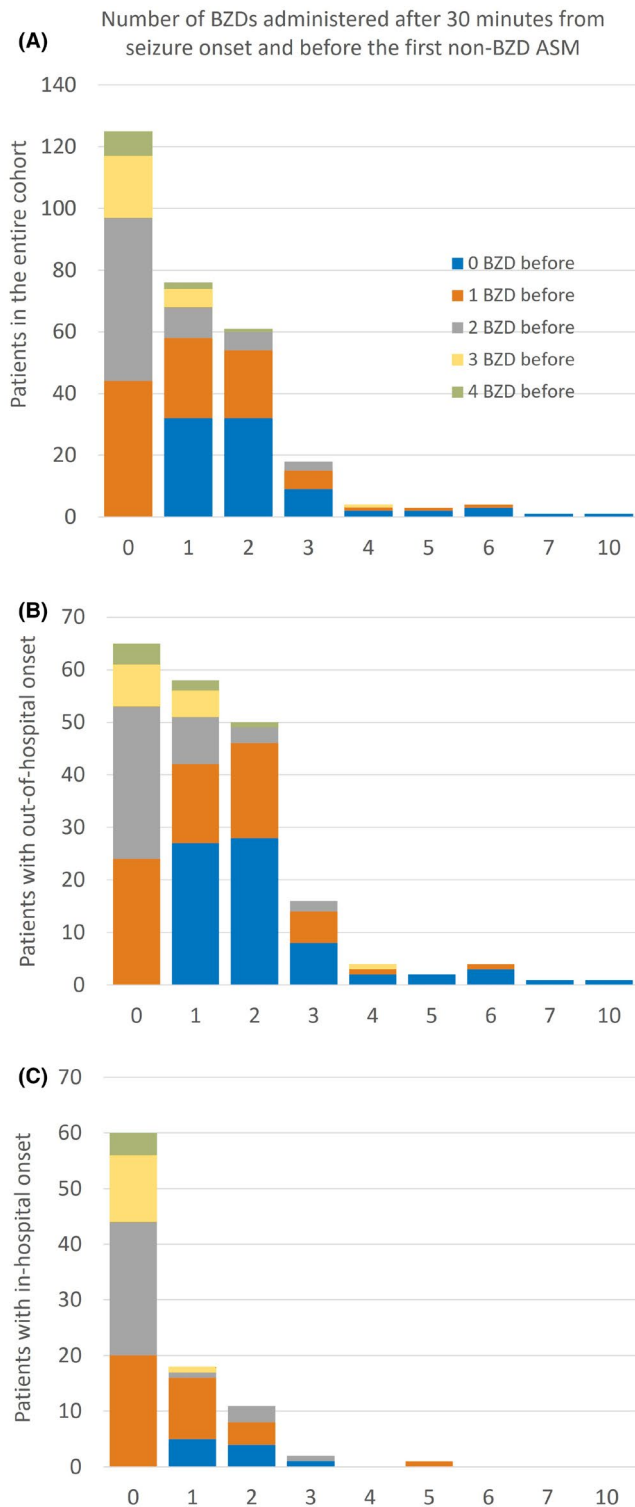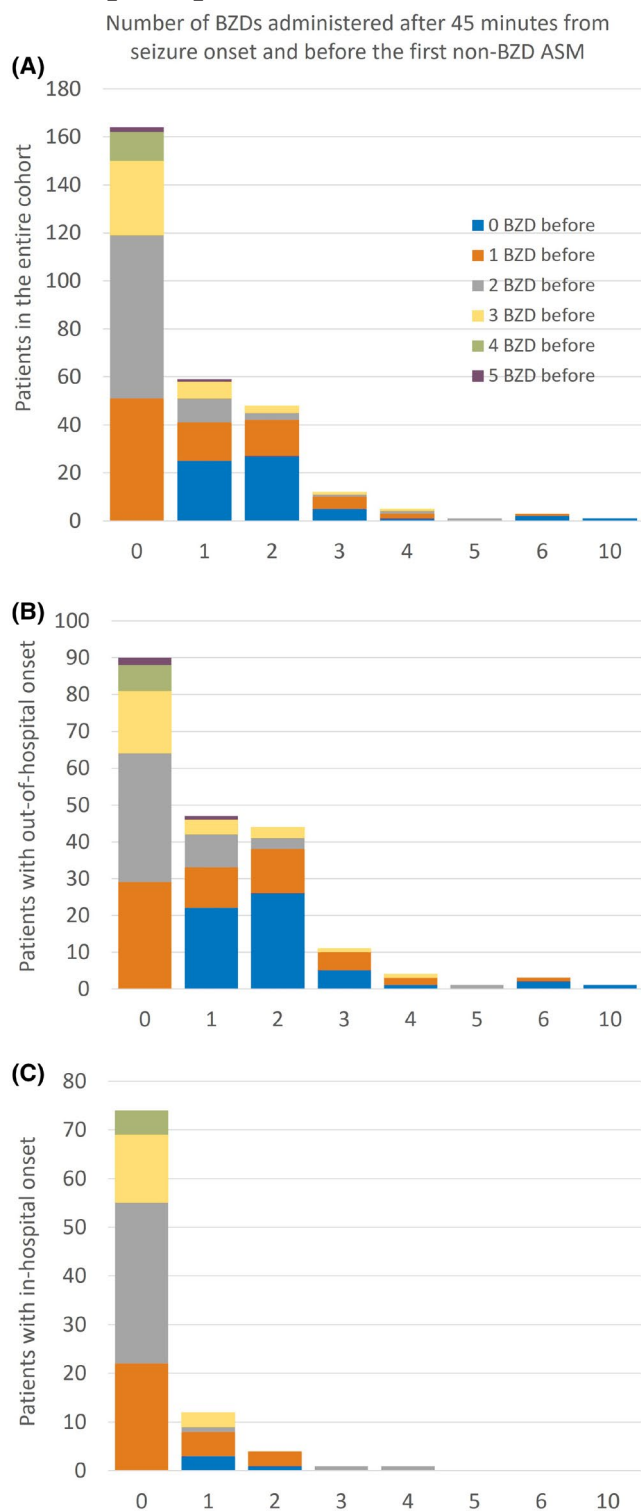
(A) Number of BZDs administered after 30 minutes from seizure onset and before the first non-BZD ASM

Patients in the entire cohort

- 0 BZD before
- 1 BZD before
- 2 BZD before
- 3 BZD before
- 4 BZD before

(B) Patients with out-of-hospital onset

(C) Patients with in-hospital onset

FIGURE 2 Bar graphs representing the number of benzodiazepines (BZDs) administered after 30 min from seizure onset and before the first non-BZD antiseizure medication (ASM) in the entire cohort (A), subpopulation of patients with out-of-hospital status epilepticus onset (B), and subpopulation of patients with in-hospital status epilepticus onset (C). The colors of the stacked bars represent the number of BZDs already administered during the first 30 min after seizure onset. For example, in the entire cohort (A), 76 patients received one BZD after the first 30 min from seizure onset and before the first non-BZD ASM (second bar); of those 76 patients, 32 patients had not received any BZD within the first 30 min (blue section of the second bar), 26 patients had received one BZD (orange section of the second bar), 10 patients had received two BZDs (gray section), et cetera

BZD as the best first-line option when treatment delays are the norm in the field. Future SE guidelines may consider the time from seizure onset when deciding on the first rescue treatment to administer. An example may be starting with early polytherapy (a BZD plus a non-BZD ASM) in SE that has persisted for longer than 30 min.[49] Improved prehospital management, faster transition to non-BZD ASM, improved handoff at points of care, and potentially novel treatment approaches such as catch-up dosing or early polytherapy, among others, may provide future opportunities for care improvements in selected patients with rSE.

Results need to be interpreted in the setting of data acquisition. Our population is not representative of all children with seizures or SE, but only of children with witnessed convulsive SE onset who did not respond to initial ASMs and were treated at large academic centers. We do not have information on the proportion of EMS allowed to administer a non-BZD ASM, the proportion of patients with intravenous access to administer second-line ASMs, or the number of nodes patients transitioned through (outside hospital locations such as primary care centers, the number of EMS or hospital transfers, etc.), which could be used to assess whether more nodes of care affect the transition from BZD to non-BZD ASMs. We have information on the location of ASM administration, but this does not consider other potential transient locations where treatments were not given. We did not include the etiology of SE in the model because it is often unknown in the early stages of seizure occurrence and rarely conditions BZD usage; past medical history, such as prior epilepsy diagnosis and prior SE event, may be a greater determinant of BZD usage and was included in our multivariate models. As factors influencing variability may be very extensive (variability in clinical practice over time and among regions and providers at the same point in time -different EMS systems, hospitals, doctors, etc.), our sample size is not sufficiently large to consider all potential effects while

patient outcomes.[50] Treatment algorithms are commonly restarted instead of continued in the transfer of care (from caregivers to EMS, emergency department, and referral hospital), leading to further delays in ASM transition. Our findings suggest a need for optimized prehospital care and more effective patient handoffs involving a standardized practice for the management of SE. Our results may also provide baseline data for questioning the prominence of

Number of BZDs administered after 45 minutes from seizure onset and before the first non-BZD ASM

(A)

(B)

(C)

FIGURE 3 Bar graphs representing the number of benzodiazepines (BZDs) administered after 45 min from seizure onset and before the first non-BZD antiseizure medication (ASM) in the entire cohort (A), subpopulation of patients with out-of-hospital status epilepticus onset (B), and subpopulation of patients with in-hospital status epilepticus onset (C). The colors of the stacked bars represent the number of BZDs already administered during the first 45 min after seizure onset. For example, in the entire cohort (A), 59 patients received one BZD after the first 45 min from seizure onset and before the first non-BZD ASM (second bar); of those 59 patients, 25 patients had not received any BZD within the first 45 min (blue section of the second bar), 16 patients had received one BZD (orange section of the second bar), 10 patients had received two BZDs (gray section), et cetera

SE. BZD dosing, types, routes of administration, and effect on outcome were already addressed in another study from our original cohort.[24]

5 | CONCLUSIONS

In this multicenter study on pediatric rSE in the United States and Canada, about one third of patients received more than two BZD doses before transitioning to non-BZD ASMs, and more than half of patients received BZD doses after 30 min from seizure onset. Out-of-hospital seizure onset and intermittent SE were associated with the failure to escalate from BZDs to non-BZD ASMs. Specifically, patient handoffs between prehospital and in-hospital settings may hinder the escalation of ASM due to restarts of treatment algorithms and may offer an opportunity for future intervention and improvement in care.

CONFLICT OF INTEREST
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maintaining the robustness of our model. Lastly, the 45-min threshold may be arguable, as we do not have extensive and conclusive literature about the exact cutoff and conditions for BZD resistance in humans. We decided to choose only one additional and acceptable threshold to prevent multiple testing. Despite these challenges, our data provide information on medication escalation patterns in a large dataset as well as opportunities for improvement in

AUTHOR CONTRIBUTIONS

Theodore Sheehan and Marta Amengual-Gual participated in drafting and revising the manuscript for content, including medical writing, study concept and design, data acquisition, analysis and interpretation of data, statistical analysis, and study supervision or coordination; Bo Zhang and Kush Kapur participated in revising the manuscript for content, study concept and design, analysis and interpretation of data, and study supervision or coordination. All other authors participated in revising the manuscript for content, including medical writing, study concept and design, data acquisition, interpretation of data, and study supervision or coordination. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

DATA AVAILABILITY STATEMENT

All relevant data, statistical analyses, and results can be found in File S2 (https://github.com/tsheehan01/BZD_Transition).

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