

Continuous Refractory Status Epilepticus

RESULTS

Characteristics of Study Subjects. One hundred six patients (59% males) had continuous rSE with a median (p_{25} - p_{75}) age of 3.1 (1.9 – 9.3) years. Among this population, 79 (75%) rSE episodes started out-of-hospital and 27 (25%) started in-hospital. The first BZD was administered at home in 24 (23%) patients, by EMS in 28 (26%) patients, at a non-pSERG study hospital in 20 (19%) patients, and at a pSERG study hospital in 38 (32%) patients. The main demographic and clinical features are summarized in Table 1.

Main Results

BZDs administered before first non-BZD ASMs. The median (p_{25} - p_{75}) number of BZD doses given before non-BZD ASMs was 2 (2 - 3) (Table 2). The time from seizure onset to first BZD was 15 (7 – 28) minutes. Fifty-six of 106 (53%) patients received at least one BZD beyond 30 minutes following seizure onset and before the first non-BZD ASM (Figure 1, Table 3), and 38 of 106 (36%) patients received at least one BZD administered after 45 minutes from seizure onset and before the first non-BZD ASM (Table 4). Patients with out-of-hospital rSE onset received similar BZD doses to patients with in-hospital rSE onset [2 (1-3) versus 2 (1-3), $p=0.30$], received their first BZD later [17 (10 – 30) minutes versus 9 (5 – 15) minutes, $p < 0.0001$], had a greater proportion of patients receiving at least one BZD after 30 minutes from seizure onset and before the first non-BZD ASM [49 of 79 (62%) versus 7 of 27 (26%); odds ratio from Fisher's exact test 0.22, 95% CI 0.07 to 0.61; $p < 0.002$], and a greater proportion of patients receiving at least one BZD after 45 minutes from seizure onset and prior to the first non-

BZD ASM [35 of 79 (44%) versus 3 of 27 (11%); odds ratio from Fisher's exact test 0.16, 95% CI 0.03 to 0.59; $p < 0.003$].

First non-BZD ASM. The median (p_{25} - p_{75}) time to first non-BZD ASM was 57 (36 – 77) minutes. Patients with rSE onset out of the hospital received their first non-BZD ASM later than patients with rSE onset in the hospital [60 (40 – 87) versus 40 (29 – 60) minutes, $p = 0.005$].

Opportunities for improving time to non-BZD ASMs. Based on our analyses, we describe three treatment patterns that may potentially contribute to delays in administering the first non-BZD ASM:

1) Patients with out of hospital onset not receiving any ASM prior to hospital arrival. Among 79 patients with out-of-hospital rSE onset, 28 (35%) did not receive any medication until hospital arrival. Of these 28 patients, 13 (46%) had a prior diagnosis of epilepsy and 7 (25%) had a prior episode of SE.

2) Patients receiving more than two BZDs before the first non-BZD ASM. Forty-five of 106 (43%) patients received more than two BZD doses, including 37 of 79 (47%) patients with out-of-hospital onset and 8 of 27 (30%) with in-hospital onset, [odds ratio from Fisher's exact test 0.48, 95% CI 0.16 to 1.32; $p = 0.1755$]. The third BZD dose was administered at home in one patient. All other patients received their third BZD by EMS (13 patients), at a non-pSERG study hospital (13 patients) or at a pSERG study hospital (18 patients).

3) Repeated doses of BZDs in hospital in patients who had received at least two BZDs prior to hospital arrival. Among the 52 patients who received at least two BZDs prior to hospital arrival, 12 (23%) received at least one additional BZD at hospital arrival. Among these 12 patients, 2 BZDs ($N = 6$), 3 BZDs ($N = 3$), 4 BZDs ($N = 2$), 5 BZDs ($N = 1$) were given before

hospital arrival. Despite multiple BZDs already given, all 15 patients received a BZD and not a non-BZD ASM as the first ASM in the hospital.

FIGURE

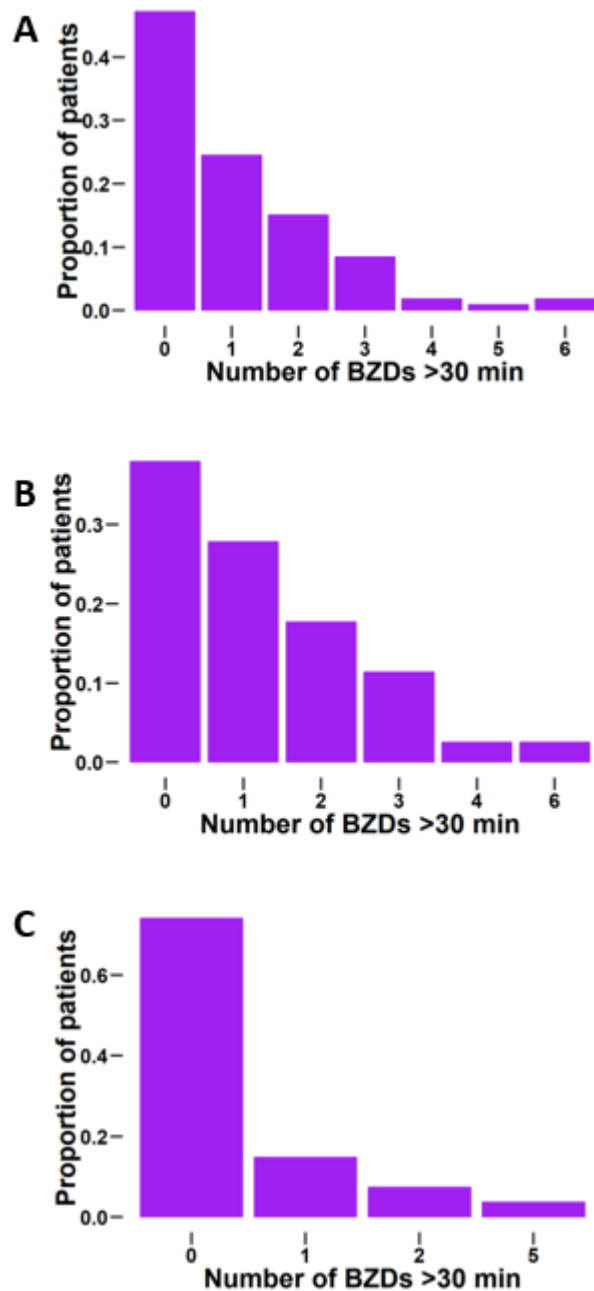


Figure 1. Number of total benzodiazepine doses administered before the first non-benzodiazepine anti-seizure medication and after 30 minutes from seizure onset. **A.** Entire cohort of patients with continuous SE. **B.** Patients with out-of-hospital onset. **C.** Patients with in-hospital onset. **Legend:** **BZD:** Benzodiazepine. **min:** Minutes.

TABLES

Table 1. Demographic and clinical characteristics.

		Entire cohort of patients with continuous SE (N = 106)	Out-of-hospital onset (N = 79)	In-hospital onset (N = 27)
Age at SE in years	Median (p ₂₅ -p ₇₅)	3.1 (1.9 – 9.3)	3.7 (1.2 – 9.1)	4.7 (1.9 – 9.0)
Sex	Male	63 (59.4%)	49 (62.0%)	14 (51.9%)
	Female	43 (40.6%)	30 (38.0%)	13 (48.1%)
Race	White	63 (59.4%)	43 (54.4%)	20 (74.1%)
	African-American	22 (20.8%)	18 (22.8%)	4 (14.8%)
	American-Indian/Alaska Native	0 (0%)	0 (0%)	0 (0%)
	Asian	2 (1.9%)	2 (2.5%)	0 (0%)
	Arabic	6 (5.7%)	5 (6.3%)	1 (3.7%)
	Hawaiian/Pacific	0 (0%)	0 (0%)	0 (0%)
	Unknown/not reported	13 (12.3%)	11 (13.9%)	2 (7.4%)
Ethnicity	Hispanic or Latino	14 (13.2%)	10 (12.7%)	4 (14.8%)
	Not Hispanic or Latino	80 (75.5%)	58 (73.4%)	22 (81.5%)
	Unknown/not reported	12 (11.3%)	11 (13.9%)	1 (3.7%)
Medical history*	DD/ID	63 (59.4%)	43 (54.4%)	20 (74.1%)
	Cerebral palsy	9 (8.5%)	5 (6.3%)	4 (14.8%)
	SE with fever	16 (15.1%)	12 (15.2%)	4 (14.8%)
	History of epilepsy	51 (48.1%)	40 (50.6%)	11 (40.7%)
	History of SE	28 (26.4%)	22 (27.8%)	6 (22.2%)
	No past neurological history	31 (29.2%)	23 (29.1%)	8 (29.6%)
Duration of SE in minutes	Median (p ₂₅ -p ₇₅)	90 (59 – 172)	98 (62 – 180)	78 (38 – 125)
Type of SE	Continuous	15 (7 – 28)	17 (10 – 30)	9 (5 – 15)
	Intermittent			
Time to first BZD in minutes from seizure onset	Median (p ₂₅ -p ₇₅)	3.1 (1.9 – 9.3)	3.7 (1.2 – 9.1)	4.7 (1.9 – 9.0)
Time to first non-BZD ASM in minutes from seizure onset	Median (p ₂₅ -p ₇₅)	63 (59.4%)	49 (62.0%)	14 (51.9%)

Legend: %: Percentage. **BZD:** Benzodiazepine. **DD:** Developmental delay. **ID:** Intellectual disability. **p₂₅-p₇₅:** Percentiles 25th and 75th. **SE:** Status epilepticus. **Non-BZD ASM:** Non-benzodiazepine anti-seizure medication.

*Percentages do not add up to 100% as patients may belong into more than one category

Table 2. Number of benzodiazepines given before the first non-ASM BZD.

Number of BZDs given before first non-BZD ASM	1	2	3	4	5	6
Entire cohort of patients with continuous SE	24 (22.6%)	37 (34.9%)	23 (21.7%)	14 (13.2%)	5 (4.7%)	3 (2.8%)
Out-of-hospital onset	18 (22.8%)	24 (30.8%)	19 (24.1%)	11 (13.9%)	5 (6.3%)	2 (2.5%)
In-hospital onset	6 (22.2%)	13 (48.1%)	4 (14.8%)	3 (11.1%)	0 (0%)	1 (3.7%)

Legend: BZD: Benzodiazepine. **non-BZD ASM:** Non-benzodiazepine anti-seizure medication.

Table 3. Number of benzodiazepines given before the first non-ASM BZD that were administered after 30 minutes from seizure onset.

Number of BZDs given before first non-BZD ASM that were administered after 30 minutes from seizure onset	0	1	2	3	4	5	6
Entire cohort of patients with continuous SE	50 (47.2%)	26 (24.5%)	16 (15.1%)	9 (8.5%)	2 (1.9%)	1 (0.9%)	2 (1.9%)
Out-of-hospital onset	30 (38.0%)	22 (27.8%)	14 (17.7%)	9 (11.4%)	2 (2.5%)	0 (0%)	2 (2.5%)
In-hospital onset	20 (74.1%)	4 (14.8%)	2 (7.4%)	0 (0%)	0 (0%)	1 (3.7%)	0 (0%)

Legend: BZD: Benzodiazepine. **non-BZD ASM:** Non-benzodiazepine anti-seizure medication.

Table 4. Number of benzodiazepines given before the first non-ASM BZD that were administered after 45 minutes from seizure onset.

Number of BZDs given before first non-BZD ASM that were administered after 45 minutes from seizure onset	0	1	2	3	4	6
Entire cohort of patients with continuous SE	68 (64.2%)	17 (16.0%)	13 (12.3%)	6 (6.7%)	1 (0.9%)	1 (0.9%)
Out-of-hospital onset	44 (55.7%)	15 (19.0%)	13 (23.7%)	6 (16.5%)	0 (0%)	1 (1.3%)
In-hospital onset	24 (88.9%)	2 (7.4%)	0 (0%)	0 (0%)	1 (3.7%)	0 (0%)

Legend: BZD: Benzodiazepine. **non-BZD ASM:** Non-benzodiazepine anti-seizure medication.