



Pharmacist involvement with antiepileptic therapy for status epilepticus in the emergency department

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ABSTRACT

Background

Despite there being an estimated 50,000–150,000 emergency department (ED) visits per year related to status epilepticus, there are limited data regarding pharmacist involvement in patient care. The purpose of this study was to evaluate differences in time to antiepileptic drug (AED) administration and appropriate AED use and dose when a pharmacist was present or not.

Methods: Retrospective, single-center, observational study of adult status epilepticus patients presenting to the ED between January 2018 through July 2020. The primary outcome was time to AED administration. Secondary outcomes included occurrence of appropriate AED selection and dose, escalation of care, length of stay (LOS), and 30-day mortality. Wilcoxon rank-sum was used for continuous variables and nominal data was analyzed by Chi-square or Fisher's Exact test, as appropriate.

Results: Twenty patients were included; 13 in the pharmacist-present and seven patients in the no-pharmacist-present groups. Median time to first and second AED was 26 min (IQR 17–177) versus 37 min (IQR 21–206), $p = 0.58$, and 51 min (IQR 30–221) versus 171 min (IQR 99–433), $p = 0.07$, in the pharmacist-present and no-pharmacist-present groups, respectively. Although there was no difference between groups for appropriate AED selection, those in the pharmacist-present group received a higher median dose of lorazepam equivalents (2.5 mg [IQR 2–4] vs 2 mg [IQR 2–2]; $p = 0.04$) and were more likely to receive at least 4 mg of lorazepam equivalents (38% vs 0%; $p = 0.11$). There were no differences in hospital LOS or 30-day mortality.

Conclusion: Pharmacist presence during status epilepticus patient management was associated with a clinically significant reduction in time to administration of AEDs. Medication doses were more guideline adherent and more patients received a lorazepam dose of at least 4 mg compared to when a pharmacist was not present.

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1. Introduction

There are an estimated 2.5 million emergency department (ED) visits per year related to seizures and 50,000–150,000 ED visits per year related to status epilepticus (SE) [1]. The American Epilepsy Society defines SE as 5 min or more of continuous seizure activity or two or more sequential seizures without full recovery of consciousness between episodes [2]. SE is a neurologic emergency and may present in several forms that must be quickly identified by the treating clinician due to a mortality rate of up to 30% in adult patients [2].

The goal of therapy for SE is rapid termination of both clinical and electrical seizure activity as this reduces associated morbidity and

mortality [2]. The 2016 American Epilepsy Society Guideline for the Treatment of Convulsive Status Epilepticus recommends a benzodiazepine as the first AED of choice during the initial therapy phase [2]. During the second-line therapy phase, there is no evidence-based preference of AED. Options include intravenous (IV) fosphenytoin, levetiracetam, or valproic acid [2].

In the ED setting, emergency medicine pharmacists (EMPs) are involved with a variety of activities such as bedside clinical services, interdisciplinary training and education, and performance improvement aimed at optimizing patient care [3]. Several studies have shown the direct clinical impact a pharmacist can have such as shortening time to critical medication administration, increasing the proportion of patients receiving guideline-adherent therapy, and reducing return ED visits [3–6]. A meta-analysis of adult and pediatric patients treated for SE in a variety of settings found that the median delay to first AED was 30 to 70 min, 1 to 2 h delay for second AED, and 2.5 to 3 h delay for third

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AED [7]. Patients treated in the ED within 1 h of seizure onset had better recovery than those beyond 1 h of onset [7]. Despite evidence that pharmacist involvement in other time-dependent emergencies reduces time to recommended medication administration, there are no studies assessing pharmacist involvement in SE management [3–6]. The purpose of this study was to evaluate the clinical impact of EMP involvement in the care of SE patients.

2. Methods

This was a retrospective, single-center, observational study that compared the management of AED therapy for patients presenting to the University of Chicago Medicine (UCM) ED in SE when an EMP was and was not present from January 1, 2018 to July 31, 2020. The study protocol was accepted by the institution's Chief Quality Determination Reviewer and did not require Institutional Review Board oversight as it was deemed quality improvement.

Patients were identified with a generated list of ICD10 codes for SE and concomitant receipt of an electroencephalogram (EEG) order while in the ED. Identified patients were then screened for inclusion via retrospective chart review. Patient protected health information was secured in a password protected RedCap database. Patients were included if they were at least 18 years of age and met the American Epilepsy Society's definition of SE [2]. Eligible patients were divided into a pharmacist-present or a no-pharmacist-present group depending on the date and time of presentation which was matched with the EMP schedule. Patients were excluded if they had a code stroke activation during their ED stay when an EMP was not scheduled because pharmacy residents respond to all code strokes 24 h per day, seven days a week and it would not be known whether they remained present for seizure management. Other exclusion criteria included pregnancy and documented concern for neurogenic seizures due to differing management strategies.

EMPs provide pharmacy services 20 h per day, seven days a week in the UCM ED. All first and second-line AEDs are stocked within an automated dispensing cabinet in the ED. Benzodiazepines are given undiluted via intravenous push or intramuscular injection whereas second-line agents are admixed by the EMP at bedside. When an EMP is not present, the central hospital pharmacy prepares second-line AEDs. In addition to admixing medications at the bedside, EMPs are routinely involved with treatment decisions, timing of escalation of care, locating IV infusion pumps, and setting up medications on pumps to ensure appropriate administration.

Demographic data, primary, and secondary outcome variables were abstracted by one investigator using a standardized database and data dictionary. Demographic data included median age, gender, ethnicity, documented history of seizure disorder, antiepileptic(s) prescribed prior to presentation, and receipt of an antiepileptic prior to hospital arrival. This information was obtained via chart review of what was available in the patient's electronic medical record. Patients were followed for up to 30 days following initial ED presentation.

The primary outcome of this study was time to AED administration, defined as the difference in time between ED arrival and documented AED administration. Secondary outcomes included appropriateness of AED selection, appropriateness of AED dosing, median dose of lorazepam equivalents administered, proportion of patients receiving at least 4 mg of lorazepam equivalents, escalation of care (intubation rates, refractory treatment, intensive care unit (ICU) admission), ED length of stay, hospital length of stay, and 30-day mortality. Refractory SE was defined as failing one benzodiazepine and one additional AED at therapeutic doses. Thirty-day mortality was determined by documentation of death in the electronic medical record within 30 days of the patient's index ED visit. The safety outcome evaluated was the occurrence of hypotension within 60 min of documented first-line AED administration, which was defined as a systolic blood pressure less than 90 mmHg or a diastolic blood pressure less than 60 mmHg.

Appropriate first, second, and third-line therapies can be seen in Table 1. To maintain consistency, appropriate maximum doses were based on recommendations provided in the American Epilepsy Society's Guideline [2]. All benzodiazepines were converted to lorazepam equivalents for analysis and equivalent doses were as follows: lorazepam 1 mg to midazolam 2 mg to diazepam 5 mg.

All statistical analysis was evaluated utilizing STATA software, version 15.0 (StataCorp). Non-normally distributed continuous data was analyzed by Wilcoxon rank-sum test and nominal data was analyzed by Chi-square test or Fisher's exact test.

3. Results

Between January 2018 and July 2020, 156 patients were evaluated with 20 patients identified for inclusion. Reasons for exclusion are listed in Fig. 1. There were 13 patients analyzed in the pharmacist-present group and seven patients analyzed in the no-pharmacist-present group. Median age across groups was 53 years old (IQR 39–66), 55% of the total patients enrolled were male, 50% had a documented history of seizure disorder, and 60% had an AED prescribed prior to presentation. There were no statistically significant differences between baseline characteristics (Table 2).

When compared to the no-pharmacist-present group, the pharmacist-present group's median time to first-line AED was 26 min (IQR 17–177) versus 37 min (IQR 21–206; $p = 0.58$), time to second-line AED was 51 min (IQR 30–221) versus 171 min (IQR 99–433; $p = 0.07$), and time to third-line AED was 205 min (IQR 96–416) versus 335 min (IQR 0; $p = 0.69$) (Table 3). Secondary and safety outcomes are displayed in Table 4. Notably, patients in the pharmacist-present group received higher and more guideline-adherent doses of benzodiazepines.

4. Discussion

In this study, time to administration of first, second, and third-line AEDs was reduced in the presence of an EMP. Although these findings were not statistically significant, possibly due to type II error, it can be argued that they are clinically significant. The quicker time to AED administration in the presence of an EMP can likely be explained by bedside admixing of AEDs and involvement in decision making for escalation of care.

Table 1
Appropriate first, second, and third-line AED therapies.

Place in therapy	Medication
First-line	• IV lorazepam 0.1 mg/kg ◦ Maximum dose 4 mg
	• IM midazolam 0.3 mg/kg or IV 0.2 mg/kg ◦ Maximum dose 10 mg
	• IV diazepam 0.3 mg/kg ◦ Maximum dose 10 mg
Second-line	• IV levetiracetam 40 to 60 mg/kg ◦ Maximum dose 4500 mg
	• IV fosphenytoin 20 mg PE/kg ◦ Maximum dose 1500 mg PE
	• IV valproic acid 40 mg/kg ◦ Maximum dose 3000 mg
Third-line	• Different agent from the second-line therapy group • Anesthetic doses of midazolam, propofol, pentobarbital, or thiopental

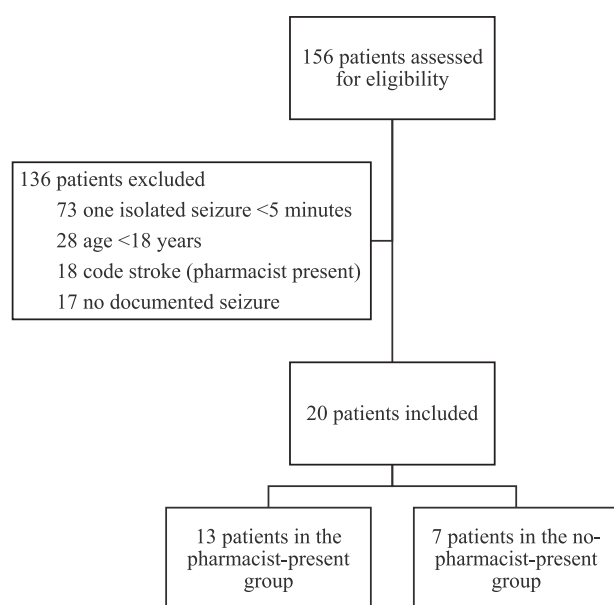


Fig. 1. Patient selection.

Increasing delays to AED administration have been observed in the setting of refractory SE [7]. Pharmacists have been shown to improve time to administration of medications during a variety of time-dependent emergencies [3,6]. A retrospective analysis of in-hospital cardiac arrests found higher compliance with advanced cardiac life support guidelines in the presence of a pharmacist (59.3% vs 31.9%; $p = 0.03$) [4]. Another retrospective study done in the ED of a comprehensive stroke center compared the management of acute ischemic stroke patients in the presence and absence of a pharmacist [5]. The authors found the door-to-needle time for fibrinolytic therapy was significantly shorter in the presence of a pharmacist (69.5 min vs 89.5 min; $p = 0.0027$) [5]. Our results are consistent with and expand upon prior research findings highlighting the benefit of EMPs.

In terms of secondary outcomes, presence of an EMP led to higher median total lorazepam equivalents administered with no difference in rates of hypotension. Median ED length of stay was significantly shorter and percentage of ICU admissions was significantly higher in

the pharmacist-present group which is revealing of a more critically ill patient population.

Strengths of this study were the strict enrollment criteria which ensured inclusion of true SE and its generalizability to centers with EMP services. Patients with isolated seizures commonly present to the ED, however, SE is a neurologic emergency dependent on timely care and is an area in need of more research. Centers with established pharmacy services can apply these findings by ensuring their EMP is involved in bedside care, shared decision making, and procurement of medications for this patient population.

Limitations include this being a retrospective review of a single center which does not fully capture the variability in treatment of SE patients nor the true impact an EMP may have. Low enrollment was a result of few patients meeting the guideline definition for SE [2] and far more presenting following one isolated seizure lasting less than five minutes in duration. There was no way to truly determine the level of involvement of the EMP in each individual case since the patient's ED arrival was only crossmatched with the EMP schedule. It is possible that there were cases that occurred in which the scheduled EMP was not involved with due to competing clinical responsibilities and, conversely, it is possible that a case occurred immediately before or after a shift that an EMP was involved with, but this was not captured.

The primary outcome was time to AED and, although we found a difference in the presence of an EMP, there are several potential confounders. These include the timing of care for the no-pharmacist-present group which occurred during overnight hours when resources are known to be limited. Also, it seems that the pharmacist-present group was a more critically ill population based on the shorter ED LOS and higher ICU admission rates. It is possible that care was escalated quicker in this patient group due to the severity of illness alone. AEDs were prepared outside of the ED when an EMP was not present building in inherent delays and potentially increasing the effect size. Administration of a pre-hospital benzodiazepine may also confound the time to administration of first AED in the ED. Only one patient from each group in our study was given a benzodiazepine prior to ED arrival. This is less than reported in the ESETT trial where 57% of patients received a benzodiazepine prior to hospital arrival [8]. In our study, the doses administered pre-hospital were suboptimal, therefore both patient groups would have required an immediate repeat benzodiazepine dose at ED presentation and this should not have effected time to AED.

In order to more accurately capture the impact of an EMP in the management of SE, multi-center studies with larger sample sizes should

Table 2
Baseline characteristics.

Variable	Pharmacist-present group (n = 13)	No-pharmacist-present group (n = 7)	p-Value
Median age, years (IQR)	54 (39–69)	49 (31–63)	0.76
Male, n (%)	6 (46)	5 (71)	0.37
Female, n (%)	7 (54)	2 (29)	0.37
Race and Ethnicity, n (%):			
African American	6 (46)	4 (57)	0.48
Hispanic	0	1 (14)	
Caucasian	1 (8)	0	
Unknown	6 (46)	2 (29)	
Documented history of seizure disorder, n (%)	4 (31)	6 (86)	0.06
Antiepileptic medication prescribed prior to presentation, n (%)	6 (46)	6 (86)	0.16
Received antiepileptic medication prior to hospital arrival, n (%)	1 (8)	1 (14)	1

Table 3
Primary Outcome

Variable	Pharmacist-present group (n = 13)	No-pharmacist-present group (n = 7)	p-Value
Median time to first-line AED, minutes (IQR)	26 (17–177)	37 (21–206)	0.58
Median time to second-line AED, minutes (IQR)	51 (30–221)	171 (99–433)	0.07
Median time to third-line AED, minutes (IQR)	205 (96–416)	335 (0)	0.69

Table 4
Secondary and Safety Outcomes

Variable	Pharmacist-present group (n = 13)	No-pharmacist-present group (n = 7)	p-Value
Appropriate selection:			
First-line AED, n (%)	11/13 (85)	7/7 (100)	0.52
Second-line AED, n (%)	11/12 (92)	4/5 (80)	0.51
Third-line AED, n (%)	7/8 (88)	1/1 (100)	1
Appropriate dose:			
First-line AED, n (%)	3/13 (23)	0	0.52
Second-line AED, n (%)	3/12 (25)	1/5 (20)	1
Third-line AED, n (%)	4/8 (50)	0	1
Benzodiazepine administration:			
Lorazepam equivalents in the ED, median mg (IQR)	2.5 (2–4)	2 (0)	0.04
Received at least 4 mg of lorazepam equivalents, n (%)	5/13 (38)	0	0.11
Number of benzodiazepine doses, median n (IQR)	2 (1–2.5)	1 (0)	0.09
Safety:			
Hypotension within 60 min of first-line AED administration, n (%)	5/13 (38)	1/7 (14)	0.35
Intubated in ED, n (%)	1/13 (8)	0	1
Refractory status epilepticus, n (%)	1/13 (8)	0	1
30-day mortality, n (%)	1/13 (8)	0	1
Disposition/LOS:			
ICU admission, n (%)	7/13 (54)	0	0.04
ED length of stay, median minutes (IQR)	431 (340–568)	679 (570–992)	0.006
Hospital length of stay, median days (IQR)	3 (2–9)	3 (1–4)	0.18

be done. This study is hypothesis generating and adds to the literature by suggesting that patients were provided better optimized care as shown by improved time to AED administration and more appropriate first-line AED dosing in the presence of an EMP.

5. Conclusion

Management of SE patients in the presence of an EMP was associated with an improved time to medication administration and more appropriate dosing of benzodiazepines.

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Paula Gawedzki: Writing – review & editing, Writing – original draft, Visualization, Software, Resources, Methodology, Investigation,

Formal analysis, Data curation. **Laura Celmins:** Writing – review & editing, Supervision, Project administration, Methodology. **Daniel Fischer:** Writing – review & editing, Validation, Supervision, Resources, Project administration, Methodology.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

- [1] G. Clayton, O. Bailey. Seizures & status epilepticus. Society of academic emergency medicine: clerkship directors in emergency medicine. <https://www.saem.org/cdem/education/online-education/m4-curriculum/group-m4-neurology/seizure-status-epilepticus> Updated: November 2019.
- [2] Glauser T, Shinnar S, et al. Evidence-based guideline: treatment of convulsive status epilepticus in children and adults: report of the guideline committee of the American epilepsy society. *Epilepsy Curr.* 2016;16(1):48–61.
- [3] Morgan S, Acquisto N, et al. Clinical pharmacy services in the emergency department. *Am J Emerg Med.* 2018;36(10):1727–32.
- [4] Draper HM, Eppert JA. Association of pharmacist presence on compliance with advanced cardiac life support guidelines during in-hospital cardiac arrest. *Ann Pharmacother.* 2008;42:469–74.
- [5] Gosser RA, Arndt RF, Schaafsma K, Dang CH. Pharmacist impact on ischemic stroke care in the emergency department. *J Emerg Med.* 2016;50:187–93.
- [6] Attwood RJ, Garofoli AC, Baudoin MR, Smith VD, Woloszyn AV, Berg AK, et al. Impact of emergency department clinical pharmacist response to an automated electronic notification system on timing and appropriateness of antimicrobials in severe sepsis or septic shock in the emergency department. *Ann Emerg Med.* 2012;60:S118.
- [7] Hill C, et al. Timing is everything: where status epilepticus treatment fails. *Ann Neurol.* 2017;82(2):155–65.
- [8] Kapur J, Elm J, et al. Randomized trial of three anticonvulsant medications for status epilepticus. *NEJM.* 2019;381(22):2103–13.