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Early withdrawal of non-anesthetic antiepileptic drugs after successful termination of nonconvulsive seizures and nonconvulsive status epilepticus

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ABSTRACT

Purpose: Multiple antiepileptic drugs (AEDs) are often necessary to treat nonconvulsive seizures (NCS) and nonconvulsive status epilepticus (NCSE). AED polypharmacy places patients at risk for adverse side effects and drug–drug interactions. Identifying the likelihood of seizure relapse when weaning non-anesthetic AEDs may provide guidance in the critical care unit.

Method: Ninety-nine adult patients with successful treatment of electrographic-proven NCS or NCSE on continuous critical care EEG (CCEEG) monitoring were identified retrospectively. Patients were determined to undergo an AED wean if the number of non-anesthetic AEDs was reduced at the time of discharge compared to the number of non-anesthetic AEDs at primary seizure cessation. Primary outcome was recurrent seizures either clinically or by CCEEG during hospitalization. Secondary outcome measures included hospital length of stay and discharge disposition.

Results: The rate of recurrent seizures in the wean group was not statistically different when compared to the group that did not undergo an AED wean (17% vs. 13%, respectively; $p = 0.77$). The wean group had a median value of 4 (IQR: 3–4) non-anesthetic AEDs at the time of primary seizure cessation compared with 3 (IQR: 2–3) in the non-wean group ($p < 0.0001$). However, both groups had similar values of AEDs at discharge (median of 2 (IQR: 2–3) vs. 3 (IQR: 2–3) for wean and non-wean groups respectively; $p = 0.40$). Discharge disposition (favorable, acceptable, or unfavorable) was similar between groups ($p = 0.32$).

Conclusions: Early weaning of non-anesthetic AEDs does not increase the risk of recurrent seizures in patients treated for NCS or NCSE during their hospitalization.

1. Introduction

Nonconvulsive seizures (NCS) and nonconvulsive status epilepticus (NCSE) are frequently observed in critically ill patients with acute brain injury admitted to the neurologic intensive care unit (NICU). The incidence of NCS and NCSE ranges between 8 and 48% depending on the patient population studied [1–8]. The mortality rate of neurologically critically ill patients afflicted with NCSE is 18–57% [9,10] while the presence of NCS is associated with a mortality rate of 33% [10]. Although the presence of NCS does not independently affect mortality, it has been found that the duration of NCS is associated with an increase in mortality [10] and that increasing seizure burden worsens cognitive and functional outcomes [11]. Therefore, prompt identification and appropriate treatment are essential, requiring CCEEG monitoring since seizures are nonconvulsive in 92% of critically ill patients whose hospital course is complicated by NCS or NCSE [1].

Multiple AEDs are often required to treat NCS and NCSE. First-line anticonvulsants fail to terminate status epilepticus (SE) in 31–50% of cases [12,13]. Although the optimal treatment for NCS and NCSE is unknown, various anesthetic and non-anesthetic AEDs are available to treat seizures in the critically ill patient population [14,15]. It is standard practice to add additional AEDs when current treatment regimens fail. After successful seizure control, AED polypharmacy may lead to adverse side effects, drug–drug

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interactions between AEDs and non-AEDs, and excessive cost for patients after hospital discharge if their polypharmacy regimen is continued. Common AED side effects include dizziness, fatigue, nausea and cognitive dysfunction [16]. AED weaning after successful seizure control may avoid or minimize these complications. The topic of AED withdrawal after successful epilepsy surgery has been evaluated in several studies and surveys [17–24]. However, to the best of our knowledge, there have been no studies evaluating the safety and efficacy of AED withdrawal after sustained seizure control in critically ill patients.

The goal of this retrospective study was to determine whether early withdrawal of non-anesthetic antiepileptic drugs after successful termination of NCS/NCSE resulted in re-emergence of seizures. Secondary goals included assessment of whether AED withdraw predicts hospital length of stay, favorable discharge disposition and need for repeat CCEEG monitoring. This information could help guide management of more expedited AED withdraw given the adverse side effect profile of AEDs.

2. Methods

Permission to complete this retrospective study was first obtained from the Duke Institutional Review Board. All adult patients older than 18 years admitted to Duke University Medical Center from January 1, 2010 to January 1, 2016 who underwent CCEEG monitoring were retrospectively identified using the Duke DEDUCE database. Basic patient information including age, sex, indication for EEG, and admission diagnosis were collected from the hospital electronic medical record. Information regarding the presence of electrographic seizures and EEG findings were collected from daily CCEEG procedural reports contained within the electronic medical record. The total amount of time spent with seizures on CCEEG (in days) was collected from the daily CCEEG reports. Additional information regarding dosing and timing of non-anesthetic AEDs were obtained from the medication administration record (MAR). Given the nature of the patient population, a percentage of patients were exposed to intravenous anesthetic drugs (IVADs) including midazolam, propofol and pentobarbital, to control refractory non-convulsive status epilepticus. Daily progress notes were reviewed to evaluate the indication for CCEEG monitoring as well as for information regarding medical complications. Consent was not obtained for review of prior EEG records and medical records of these patients as patients were discharged prior to analysis. All identifying information was removed from the data prior to its use.

Patients were determined to undergo an AED wean if the number of non-anesthetic AEDs was reduced at the time of discharge compared to the number of non-anesthetic AEDs at primary seizure cessation. Seizure burden was defined by the number of days that had an EEG correlate of NCS or NCSE with a value of zero representing less than 24 h of electrographic seizure. Seizure cessation was defined as seizure freedom on CCEEG for at least 24 h and absence of intravenous anesthetic drugs (IVADs) being used to treat NCS or NCSE during that time. Patients that did not undergo an AED wean had no reduction of their non-anesthetic AED regimen. The primary outcome was recurrent seizures either clinically or by CCEEG during hospitalization. Secondary outcome measures included hospital length of stay and discharge disposition defined as favorable (home, acute rehabilitation), acceptable (skilled nursing facility (SNF), long-term acute care hospital (LTACH)) and unfavorable (death, hospice). Demographic and clinical information (including baseline EEG pattern) was gathered from the electronic medical record and compared between groups to ensure that no baseline differences were present. If an EEG report on the same patient included descriptions of both slowing (either focal or generalized) and specific wave patterns (LPDs, GPDs, SIRPIDS, SW, BS), the latter was assigned as the primary EEG finding [25].

Continuous variables, such as age and number of medical problems, were compared using the Mann-Whitney test. Categorical variables were compared with the Fisher exact test. In all cases the threshold for assessing statistical significance was set to level α=0.05. All analyses were performed with R statistical software (R Core Team) [26].

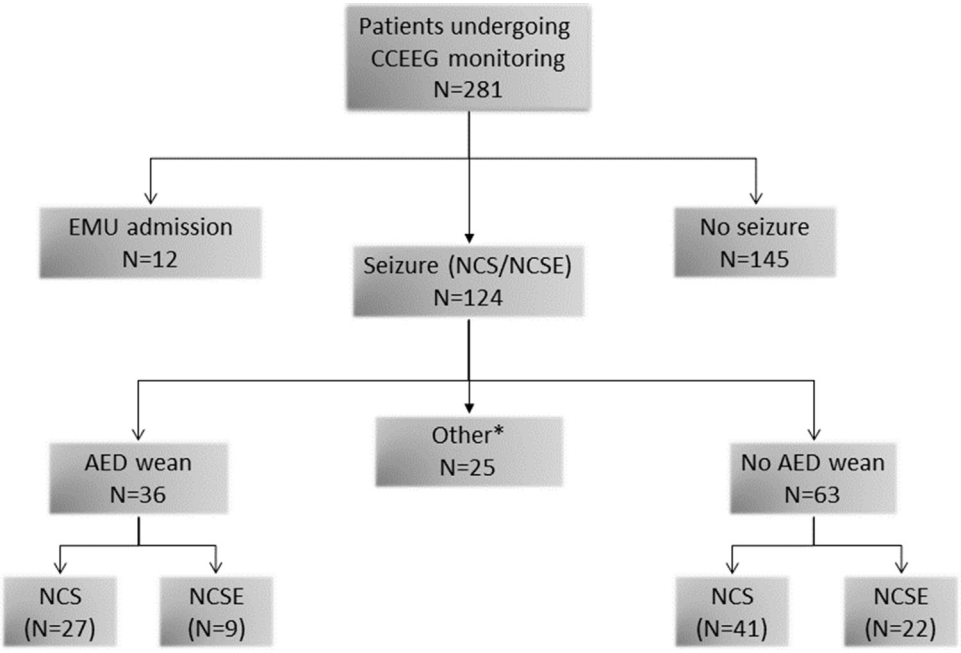

Fig. 1. Patient groups based on EEG-proven NCS/NCSE.
A total of 281 charts were reviewed retrospectively to identify patients on continuous critical care EEG (CCEEG) monitoring who underwent treatment for electrographic-proven NCS/NCSE. Of those charts, 99 were included in the final analysis. EMU, epilepsy monitoring unit. *Charts excluded because of limited access to medication records.

3. Results

In total, 281 charts were reviewed in the time period specified and meeting the criteria of patients undergoing CCEEG (Fig. 1). Of the charts reviewed, 124 patients had an EEG with ictal activity during their hospitalization defined as either NCS or NCSE per published criteria [27]. Ninety-nine of these charts were further categorized to either a wean (N = 36) or non-wean group (N = 63), while the remaining 25 charts were excluded due to limited data access since they were generated prior to initiation of the electronic medical record system. A total of 157 charts from the 281 identified were excluded either because the patient was admitted for prolonged EEG in the epilepsy monitoring unit (N = 12) or the CCEEG did not demonstrate electrographic seizures during hospitalization (N = 145).

Patient demographics were compared between the wean and non-wean groups (Table 1). There was no statistically significant difference between the two groups with respect to age (p = 0.74), gender (p = 0.68), seizure burden (p = 0.89), type of seizure (p = 0.37) and exposure to IVADs (p = 0.83). The primary etiology for seizures was determined for each patient. In the wean group, ischemic stroke was the most common (22%), followed by epilepsy-related causes (17%). This is slightly different from the non-wean group in which the majority of seizures were attributed to epilepsy (16%) or toxic/metabolic (19%) factors (Table 1). Seizures that did not fit into the most common categories were classified as "Other" (8 cases), including idiopathic and autoimmune encephalitic etiologies (Table 1).

There was no difference between wean and non-wean groups when assessed by the primary background EEG abnormality (p = 0.79, Table 1) grouped by either slowing (focal or generalized) or by a rhythmic, periodic or epileptiform pattern (LPDs, GPDs, SIRPIDs, SW and BS).

The rate of inpatient seizure relapse was not statistically different between wean and non-wean groups (17% vs. 13%, respectively; p = 0.77, Table 2). Similarly, there was no significant difference in discharge disposition between the two groups (p = 0.32) with roughly one third of each group categorized to a favorable, acceptable or unfavorable outcome (Table 2). On the other hand, there was a significantly longer hospital length of stay among patients in the wean group when compared with the non-wean group (median of 14 days vs. 11 days; p = 0.02).

The number of AEDs at the time of seizure control was significantly higher in the wean group (median of 4 AEDs, IQR: 3–4) compared to the non-wean group (3, IQR: 2–3) ($p < 0.0001$, Table 2). The number of AEDs at discharge, however was similar between the wean and non-wean groups (median 2 vs. 3, respectively; p = 0.40, Table 2).

The pattern of AED dose reduction and/or discontinuation was variable. Overall, there were eight non-anesthetic AEDs used routinely in patients with NCS or NCSE and, not surprisingly, the mode of delivery usually graduated from intravenous to oral forms during the course of the hospitalization. The AED that was most likely to first undergo dose reduction was phenytoin (Fig. 2). The AED that was most likely to be completely discontinued first during hospitalization was also phenytoin (Fig. 3).

Table 1
Patient and EEG characteristics.

Patient and EEG Characteristics	AED wean (n = 36)	No AED wean (n = 63)	P-value
Age, mean (±SD)	61.3 (±15.6)	61.0 (±14.5)	0.74
Gender, male (%)	17 (47%)	33 (52%)	0.68
IVAD use, n (%)	21 (58%)	35 (56%)	0.83
Days with seizures, median (IQR: Q1–Q3)	1 (0–2)	1 (0–2)	0.89
Type of seizure			0.37
NCS, n (%)	27 (75%)	41 (65%)	
NCSE, n (%)	9 (25%)	22 (35%)	
Primary Diagnosis, n (%)			0.40
Subdural hematoma	1 (3%)	6 (10%)	
CNS infection	0 (0%)	2 (3%)	
Hypoxic ischemic encephalopathy	4 (11%)	7 (11%)	
Postoperative	2 (6%)	3 (5%)	
Brain tumor	4 (11%)	9 (14%)	
Epilepsy-related	6 (17%)	10 (16%)	
Ischemic stroke	8 (22%)	6 (10%)	
Subarachnoid hemorrhage	0 (0%)	1 (2%)	
Toxic/metabolic	6 (16%)	12 (19%)	
Intracerebral hemorrhage	0 (0%)	4 (6%)	
Other*	5 (14%)	3 (5%)	
Focal spatial seizure, n (%)	23 (64%)	34 (54%)	0.40
Hemispheric spatial seizure, n (%)	8 (22%)	19 (30%)	0.48
Generalized spatial seizure, n (%)	6 (17%)	9 (14%)	0.78
Primary EEG finding**, n (%)			0.79
Slowing (focal and/or generalized)	6 (17%)	13 (21%)	
LPDs, GPDs, SIRPIDs, SW, BS	30 (83%)	50 (79%)	

Continuous variables are summarized with their mean (±SD), or median (IQR: Q1-Q3). Categorical variables are summarized with their frequency and percentage, n (%). *Idiopathic (n = 2, wean group; n = 2, non-wean group), autoimmune encephalitis (n = 1, wean group; n = 1, non-wean group), PRES (n = 1, wean group) or multiple sclerosis (n = 1, wean group). **If an EEG report on the same patient included descriptions of both slowing (either focal or generalized) and specific wave patterns (LPDs, GPDs, SIRPIDS, SW, BS), the latter was assigned to the primary EEG finding. Continuous variables were compared using the Mann-Whitney test, and categorical variables with the Fisher exact test. P-values less than 5% were considered statistically significant. CNS, central nervous system; Postoperative, patients postoperative from a neurosurgical procedure; LPDs, lateralized periodic discharges; GPDs, generalized periodic discharges; SIRPDs, stimulus induced rhythmic, periodic, or ictal-appearing discharges; SW, sharp-wave or spike-wave; BS, burst suppression. AED, antiepileptic drug; CNS, central nervous system; Postoperative, patients postoperative from a neurosurgical procedure; EEG, electroencephalogram; LPDs, lateralized periodic discharges; GPDs, generalized periodic discharges; SIRPDs, stimulus induced rhythmic, periodic, or ictal-appearing discharges; SW, sharp-wave or spike-wave discharges; BS, burst suppression.

Table 2
Outcome measures as a function of AED wean.

Outcome measures	AED wean (n = 36)	No AED wean (n = 63)	P-value
Inpatient seizure relapse, n (%)	6 (17%)	8 (13%)	0.77
Hospital length of stay (days), median (IQR: Q1 – Q3)	14 (11–24)	11 (6–19)	0.02
Condition on discharge, n (%)			0.32
Favorable (home, acute rehab, other)	13 (36%)	24 (38%)	
Acceptable (SNF, LTACH)	9 (25%)	23 (37%)	
Unfavorable (death, hospice)	14 (39%)	16 (25%)	
Repeat CCEEG, n (%)	12 (33%)	19 (30%)	0.82
AEDs at time of seizure control, median (IQR: Q1 – Q3)	4 (3–4)	3 (2–3)	<0.0001
AEDs at discharge, median (IQR: Q1 – Q3)	2 (2–3)	3 (2–3)	0.40

Continuous variables were compared using the Mann-Whitney test, and categorical variables with the Fisher exact test. P-values less than 5% were considered statistically significant. SNF, skilled nursing facility; LTACH, long-term acute care hospital; CCEEG, continuous critical care EEG; VA, Veteran's Affairs; Other, psychiatric facility.

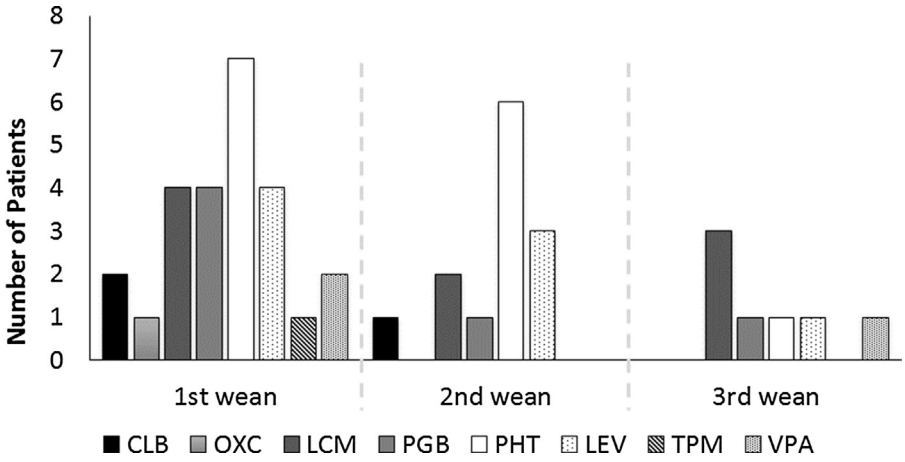

Fig. 2. AED dose reduction by medication and order.
The AED that was most likely to undergo dose reduction was phenytoin, followed by levetiracetam, lacosamide and pregabalin. CLB, clobazam; LCM, lacosamide; LEV, levetiracetam; OXC, oxcarbazepine; PGB, pregabalin; PHT, phenytoin; TPM, topiramate; VPA, valproate.

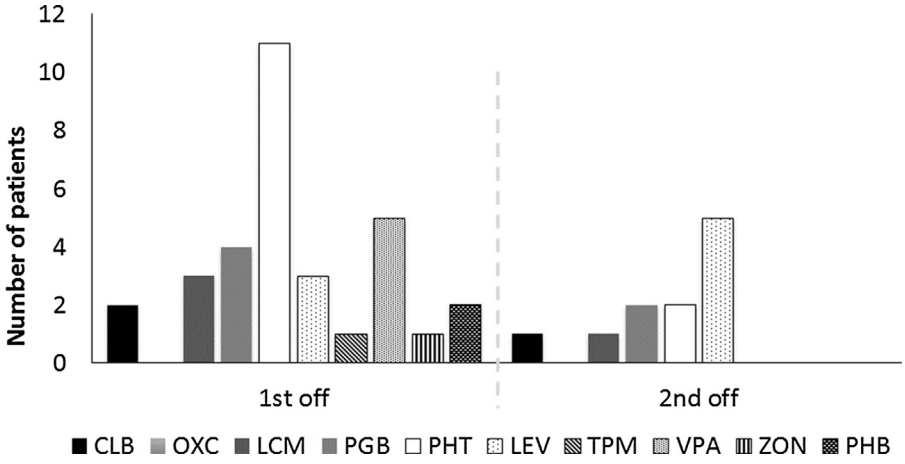

Fig. 3. AED discontinuation by medication and order.
The AED that was most likely to be completely discontinued was phenytoin, followed by valproic acid. CLB, clobazam; LCM, lacosamide; LEV, levetiracetam; OXC, oxcarbazepine; PGB, pregabalin; PHT, phenytoin; TPM, topiramate; VPA, valproate.

4. Discussion

In this study we found that following successful termination of NCS/NCSE in the ICU, partial withdraw of non-anesthetic AEDs was not associated with an increased rate of inpatient seizure relapse. Seizure cessation was defined as seizure freedom on CCEEG for at least 24 h and absence of intravenous anesthetic drugs (IVADs) being used to treat NCS or NCSE. This is the first study addressing the acute consequences of early AED withdrawal after seizure cessation in critically ill patients and emphasizes the notion that early reduction of AED dose and/or number of AEDs does not adversely impact seizure recurrence.

Essentially all previous data on discontinuing AEDs comes from the outpatient setting, namely the medically- or surgically-managed epilepsy population. In these instances, the bias is

toward an increased risk of seizure recurrence following AED discontinuation [28]. Both randomized controlled trials and prospective studies have demonstrated that adult patients with known epilepsy who continue AED treatment have relapse rates of 22–28%, compared with 41–50% in withdrawal groups [29,30] although lower seizure relapse rates of 15% have been reported in AED withdrawal groups [31]. Our study found a relapse rate of approximately 15% overall (17% and 13% in wean and non-wean groups, respectively) during the remainder of hospitalization after a seizure-free interval of at least 24 h. This lower rate compared to outpatient studies may be due, in part, to the shorter monitoring period which, by default, does not account for the long-term follow up times that were used in the outpatient population. Additionally, the acuity of seizure onset in our population is in contrast to the outpatient epileptic population which may represent a much greater seizure burden given the chronicity of their disease. Moreover, the underlying pathophysiology is quite different between the critically ill patient population in the current study which represents a diverse group of etiologies including both focal (ischemia, hemorrhage, tumor) and diffuse (infections, toxic, metabolic) lesions as compared to the epileptic population undergoing surgical or medical management.

Our data demonstrates that AED weaning did not influence patient discharge disposition, with discharges being evenly distributed between favorable (home, acute rehabilitation), acceptable (SNF, LTACH) and unfavorable (death, hospice) outcomes. Approximately one third of patients died or went to hospice, which is not surprising given that NCS/NCSE in ICU patients is associated with increased mortality and worsened outcome [32], and is in keeping with previous studies that reported mortality rates of about 30% for critically ill patients with seizures lasting greater than one hour [33]. However, the rate of poor outcomes does not appear to be influenced by AED discontinuation.

Perhaps prognosis is more a reflection of other factors such as underlying ictal pattern or seizure etiology. While some studies show that within the NCS/NCSE group, subjects with generalized ictal discharges had a worse prognosis compared to subjects with unilateral ictal discharges [34], others did not find any prognostic correlation with abnormal or epileptiform EEG [31]. In the context of AED withdrawal, a number of studies have identified factors associated with increased risk of relapse including multiple seizure types, focal epileptiform abnormalities on EEG, and worsening EEG patterns after AED discontinuation [29,35–37]. While we did not analyze outcomes based on NCS/NCSE subtypes, we did find that the primary background EEG abnormality was similar to previously published studies and did not differ between the wean and non-wean groups.

Previous studies have shown that NCS/NCSE is frequently seen with acute brain insults with an incidence ranging between 8 and 48% depending on the patient population studied [1–8]. The etiology of NCS/NCSE in our patient population was comparable to previous reports stemming from both population-based [2] and retrospective studies [38]. Stroke (including ischemic and hemorrhagic) was the most common contributor, followed by epilepsy-related, toxic metabolic, brain tumor, HIE and CNS infection [2,8,38]. Additionally we included “post-operative” condition as a risk factor for seizure occurrence whereas other groups have included “sub-therapeutic anticonvulsant drugs levels” or “drug/alcohol withdrawal” as causative factors in seizure [2].

Interestingly, we found that hospital length of stay (LOS) was longer in the group that underwent an AED wean with a median of 14 days as compared to 11 days in the non-wean group. This is in keeping with hospital LOS of 12 days previously reported among the NCS/NCSE population [34]. The longer LOS in the wean group may be due to several reasons. For one, the number of AEDs required to achieve seizure cessation was significantly higher in the wean group, therefore possibly representing a more aggressive form of NCS/NCSE. Conceivably, the higher number of AEDs could translate to more side effects and drug–drug interactions that necessitated more hospital days to resolve. Moreover, the very nature of weaning may require a longer period to establish a tailored AED regimen for an individual patient.

There are no studies to guide practice of tapering AEDs in the acute setting, particularly with respect to the order, type and speed of AED removal. In the acute setting, Rosemergy and colleagues did a retrospective study of 227 patients who presented to the emergency department, of which 12 were in status epilepticus with a subset of these requiring ICU level care [39]. For those 12 patients, a little over half of the patients getting treatment with phenytoin were not discharged on phenytoin, either due to a wean or AED change, but the specifics of the AED management were not specifically reported by the authors.

There have been numerous studies dedicated to providing evidence for the weaning of AEDs in the outpatient setting in patients with epilepsy, particularly after successful epilepsy surgery [17–24]. In a survey administered to 204 adult and pediatric epileptologists, Swisher and colleagues found that most epileptologists tapered AEDs more rapidly than suggested by previous reports with the majority stopping all AEDs completely following epilepsy surgery [23]. Additionally the European TimeToStop observational study found that early AED withdrawal did not affect long-term seizure outcome [40]. In the TimeToStop study, primidone, vigabatrin and phenytoin were most frequently reduced first. Similarly, in the current study, phenytoin was most likely to first undergo dose reduction or cessation during the acute period. This is likely due to the many known adverse side effects and drug–drug interactions with phenytoin [41].

The decision on when to wean or withdrawal medication has important implications and it is common in neurocritical care practice to wean AEDs in the acute setting to prevent adverse side effects, polypharmacy, unnecessary patient cost, and drug–drug interactions. This is typically done proactively rather than in response to a specific problem. For example, many AEDs contribute to dizziness, sedation, fatigue, and inattention [16]. Additionally, some of the older AEDs (such as phenytoin and valproate) affect hepatic enzyme metabolism which is particularly undesirable for patients taking multiple medications. In patients with traumatic brain injury, anti-seizure prophylaxis with phenytoin significantly lengthened hospital stay and significantly worsened functional outcome scores at discharge based on the Glasgow Outcome Scale and modified Rankin Scale [42]. Moreover, studies in patients with epilepsy have shown that discontinuing AEDs correlates with improved outcomes on common neuropsychiatric batteries and mood assessment scales [43].

Several limitations to this study deserve mentioning, including the retrospective design as well as the small sample size with respect to categories for the different seizure etiologies. Importantly we do not show any difference in relapse rate or discharge disposition. However, it should be noted that we did not look at long term follow up and therefore cannot comment on how acute weaning of AEDs in patients with NCS/NCSE translates to the outpatient setting. Despite this, our findings provide an important perspective when managing AEDs in critically ill patients and encourage a practice of early AED weaning which may avoid the toxic short and long-term effects of these medications.

Conflict of interest

The authors whose names are listed certify that they have no affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants;

participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

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