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Seizure Prophylaxis Guidelines Following Traumatic Brain Injury: An Evaluation of Compliance

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Objective: To determine degree of adherence to guidelines for seizure prophylaxis following traumatic brain injury (TBI). **Setting:** Tertiary care level 1 trauma center and affiliated inpatient rehabilitation facility. **Participants:** A total of 173 individuals with TBI who required inpatient rehabilitation from January 1, 2007, to December 31, 2013. **Design:** Retrospective medical record review. **Main Measures:** Overutilization rate of prophylactic antiepileptic drugs (AEDs); failure to stop rate of AED utilization upon admission to and during inpatient rehabilitation; and duration of overutilization. **Results:** Of the 173 participants included, 77 were started on seizure prophylaxis at hospital presentation and 96 were not. Of the 77 participants, 11 had a posttraumatic seizure. Of the 66 remaining, 18 participants (10.4%) were continued on AEDs for more than 7 days after injury. Of these 18 participants, 12 were continued on AEDs without indication upon admission to inpatient rehabilitation. Finally, 8 of the 12 were continued on AEDs at discharge from rehabilitation, resulting in a failure to stop rate of 66.67%. **Conclusion:** Despite existing guidelines for stopping seizure prophylaxis after TBI, some patients remain on AEDs and may be inappropriately exposed to possible medication side effects. These findings highlight the importance of communication at the time of rehabilitation transfer and the need for ongoing education about AED guidelines.
Key words: *acute*, *adherence*, *epilepsy*, *guidelines*, *head injury*, *institutional*, *pharmaceutical*, *posttraumatic*, *protocol*, *rehabilitation*

AN ESTIMATED 1.7 million traumatic brain injuries (TBIs) occur in the United States annually, with more than 275 000 patients requiring hospitalization.[1] A known complication of head trauma is the development of posttraumatic seizures (PTSs), which can be defined temporally as immediate (<24 hours following injury), early (>24 hours and ≤7 days following injury), and late (>7 days following injury).[2] PTSs occur in 5% to 7% of all hospitalized patients with TBI, although the rate increases to 11% with severe nonpenetrating TBIs and up to 35% to 50% with penetrating TBIs.[3,4] Approximately one-half to two-thirds of individuals with late PTS experience an initial seizure within the first 12 months postinjury, and more than 75% experience one by the end of the second year.[5] Risk factors for developing PTS include alcohol use, increasing age, more severe injury, extended loss of consciousness, presence of cerebral contusions, subdural hematoma, and retained bone and metal fragments after penetrating head injury.[3] Furthermore, patients who experience late PTS have been shown to have more severe disability, have lower cognition, use more dependent modes of transportation, and have lower scores on satisfaction with life scales than matched patients who do not experience late PTS.[2]

Past efforts to prevent and lessen the impacts of seizures following TBI led to the widespread use of prophylactic antiepileptic drugs (AEDs). However, subsequent research has since provided clarification on the role of AEDs in preventing early and late PTSs. For example, Temkin and colleagues[6] conducted a randomized, placebo-controlled study of phenytoin in seizure prophylaxis after TBI and demonstrated a 73% risk

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reduction in seizure rate in the first week after injury but not thereafter. The lack of sufficient evidence supporting prolonged use of AEDs in preventing late PTS after 1 week led the American Association of Neurological Surgeons (AANS) and the American Academy of Physical Medicine and Rehabilitation (AAPM&R) to establish guidelines and practice parameters for post-TBI seizure prophylaxis.[5] Specifically, both the AANS and the AAPM&R recommend the use of either phenytoin or carbamazepine in preventing early (>24 hours and <7 days following injury) but not late (>7 days following injury) PTSs.[7,8] While newer drugs such as levetiracetam are now commonly used in the prevention of early PTSs, guidelines continue to state that seizure prophylaxis beyond 1 week after TBI is not warranted.[8]

Despite this evidence, a recent retrospective observational study by Kruer and colleagues[9] using a Trauma Registry reported that of 109 patients with TBI treated in the acute care setting, 65% received prophylactic AEDs for more than the recommended 7 days. Since this was not the primary outcome measure in this study, reasons for such practice were not examined. While no studies have examined the rates of seizure prophylaxis usage for individuals with TBI undergoing inpatient rehabilitation, such clinical practice has anecdotally been seen at our inpatient rehabilitation facility. For example, we have observed individuals outside the 7-day recommended treatment window still taking AEDs at the time of inpatient rehabilitation admission and beyond. This overuse is problematic, as AEDs have been linked to undesirable side effects including additional neurobehavioral impairments beyond those caused by the underlying brain injury. Dikmen et al[10] found that phenytoin significantly impaired performance on neurobehavioral assessment 1 month after brain injury. Furthermore, in a study examining the feasibility of using levetiracetam for prevention of posttraumatic epilepsy, the most common symptoms associated with usage were fatigue, headache, somnolence, memory impairment, pain, irritability, and dizziness.[11] Therefore, it is important to comply with anticonvulsant prophylaxis recommendations regarding cessation to avoid overuse with patients following TBI.

The purpose of this study was to retrospectively examine the rate of prophylactic seizure medication usage following TBI in an acute tertiary care level 1 trauma center and affiliated inpatient rehabilitation facility from 2007 to 2013. Our aim was to determine whether guidelines for cessation of seizure prophylaxis after TBI were followed.

METHODS

Participants

We conducted a retrospective medical record review of patients enrolled in the TBI Model Systems (TBIMS) at one rehabilitation facility in the southern United States. The study was approved by the institutional review board to ensure all procedures were considered ethical. Patients were included if they met TBIMS eligibility criteria (https://www.tbindsc.org/StaticFiles/SOP/101a%20-%20Identification%20of%20Subjects.pdf) and were admitted to our rehabilitation facility from January 1, 2007, to December 31, 2013. Patients were excluded if they were not in the acute care setting for more than 7 days from injury onset, had a previous diagnosis of seizure disorder, and/or were taking an AED at the time of injury. A patient was considered as having a seizure by either electroencephalogram report or written documentation in the medical record (including progress notes or discharge summary by a physician).

Procedures

First, the physician documentation (electronic medical record and paper chart) was screened to identify patients who met the inclusion/exclusion criteria. Information collected for patients who met the inclusion criteria included demographics (ie, age, race, and sex) and injury-related information (ie, date of injury, admission Glasgow Coma Scale score, date of rehabilitation admission, and rehabilitation length of stay). In addition, seizure medication data were collected and indications for medications were noted at acute hospital admission and discharge and rehabilitation admission and discharge. Specifically, the medication administration record and discharge summaries from acute care and inpatient rehabilitation were reviewed, and all AEDs prescribed were documented, including start/stop dates and indications for use. If patients were taking AEDs for reasons other than seizure prophylaxis (ie, agitation, behavior, or moods), this was clearly documented in the data collection sheet. For patients who were continued on AEDs from acute care into inpatient rehabilitation, it was recorded whether it was appropriate or inappropriate to continue their use. The seizure medications included were phenytoin, levetiracetam, carbamazepine, and valproic acid, which are the most commonly used medications at our institution.

Data analysis

A total of 201 patient charts were reviewed for the initial analysis. A total of 173 patients were included for review, as 28 met exclusion criteria. All analyses were performed utilizing SAS Enterprise Guide v5.1 (Cary, North Carolina). Categorical variables were summarized with counts and percentages. Continuous variables were summarized with means and standard deviations or medians and interquartile ranges, as indicated. To assess the rate of seizure prophylaxis utilization during acute

care stay and inpatient rehabilitation, the following were calculated:

- *Overutilization rate*: Defined as the number of patients who were inappropriately continued on AEDs for more than 7 days postinjury divided by the total number of patients included in the study.
- *Failure to stop rate*: Defined as the number of patients who inappropriately continued on the AEDs at discharge from rehabilitation divided by the total number of patients who were inappropriately continued on AEDs at admission to rehabilitation.
- *Duration of overutilization*: Defined as the number of days (beginning 7 days postinjury) a patient was inappropriately taking AEDs in the acute care setting.

RESULTS

The mean age of the sample was 45.5 ± 19.04 years, and the majority of study participants were male (n = 123; 71%) and white (n = 103; 60%), with the remaining Hispanic (n = 31; 19%) or black (n = 31; 18%). Of the 173 participants included in this study, 77 (44.5%) were started on seizure prophylaxis at hospital presentation and 96 (55.5%) were not (see Figure 1). Of the 77 participants started on seizure prophylaxis at hospital presentation, 11 had a PTS as documented by review of the medical record. Of the 66 remaining participants, 18 were continued on AEDs for more than 7 days after injury, which resulted in an overutilization rate of 10.4% (18/173 subjects). Of the 18 patients continued on AEDs, 6 had the prophylactic AEDs stopped prior to admission to rehabilitation. The median number of days AEDs were overutilized for the 6 patients was 2 days. The remaining 12 patients were continued on AEDs inappropriately upon admission to the inpatient rehabilitation unit, and 8 of the 12 were inappropriately continued on AEDs at discharge (failure to stop rate 66.67%).

The most commonly used and overutilized drug for seizure prophylaxis was phenytoin, which was prescribed to 13 of the 18 patients continued on AED prophylaxis for more than 7 days after injury. Levetiracetam was the second most common overutilized drug, prescribed to 4 of the 18 patients. Valproic acid was overutilized in 1 of the 18 patients. No patients were prescribed carbamazepine. A comparison between demographic and injury-related characteristics based on utilization category (over, other, none) is presented in Table 1.

DISCUSSION

Current guidelines support the use of prophylactic AEDs during the first 7 days after TBI to decrease the incidence of early PTS.[5,8] However, data do not support the use of prophylactic AEDs for longer than 7 days

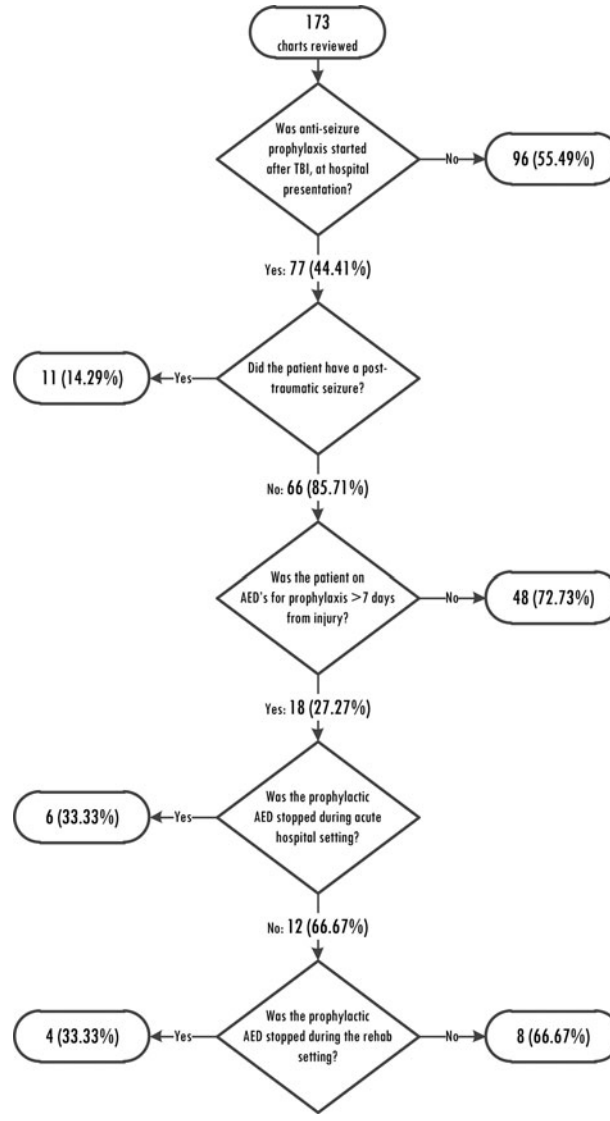

Figure 1. Schematic of seizure prophylaxis usage after hospital presentation. TBI indicates traumatic brain injury; AED, antiepileptic drug.

for preventing late PTSs.[8] In this retrospective study, we found the overutilization rate of prophylactic AEDs in the acute care setting to be 10.4%. While there is still opportunity for improvement, the overutilization rate is significantly lower than the 65% rate reported by Kruer and colleagues.[9] Current results indicate that acute care physicians at our facility (ie, trauma surgeons and neurosurgeons) were highly compliant with seizure prophylaxis guidelines and stopped the medication in a timely manner prior to admission to inpatient rehabilitation. However, if we had instead included all patients with diagnosis of TBI, regardless of acute care hospitalization location, we suspect based on clinical observation that our overutilization rate would have been much higher. Specifically, our clinical team routinely finds that TBI patients admitted to rehabilitation from outside

TABLE 1 *Demographic and injury characteristics based on utilization category*

Category	Overutilization (*N* = 18)	Other utilization (*N* = 59)	None (*N* = 96)
Age, mean (SD), y	47.22 (21.73)	43.54 (17.51)	45.76 (19.58)
Gender (male), *n* (%)	14 (77.78)	47 (79.66)	62 (64.58)
FIM Cog, mean (SD)	11.50 (5.45)	11.41 (5.93)	13.73 (6.85)
GCS, *n* (%)			
Mild	7 (38.89)	21 (35.59)	39 (40.63)
Moderate	3 (16.67)	8 (13.56)	17 (17.71)
Severe	2 (11.11)	14 (23.73)	15 (15.63)
Intubated	2 (11.11)	11 (18.64)	6 (6.25)
Sedated	4 (22.22)	5 (8.47)	19 (19.79)
PTA days, mean (SD)	23.12 (13.82)	27.84 (20.45)	19.13 (16.61)
Intracranial compression	13 (72.22)	35 (59.32)	28 (29.17)
Intracranial hemorrhage and/or contusions	18 (100)	59 (100)	83 (86.46)
Intraparenchymal fragments	3 (16.67)	2 (3.39)	2 (2.08)

Abbreviations: FIM Cog, Functional Independence Measure Cognition subscale; GCS, Glasgow Coma Scale; PTA, posttraumatic amnesia.

facilities are still taking AEDs for seizure prophylaxis weeks to months following injury. Often, these patients are recovering from severe injuries and their care has therefore been provided in several different facilities before they enter inpatient rehabilitation. Obtaining complete details of a patient's medical history in such cases is challenging, further hindering medical decision making regarding the ongoing need for AED prophylaxis.

Interestingly, of the 12 patients who were continued on seizure prophylaxis inappropriately on admission to rehabilitation, the majority (66.67%) were discharged on prophylaxis, indicating a high failure to stop rate in inpatient rehabilitation. While the reasons these patients were continued on seizure prophylaxis inappropriately are unclear, several possibilities exist. One possibility is inadequate communication between referring and accepting physicians. For example, if a patient was taking an AED at acute care discharge, the medicine could have been interpreted as clinically important and necessary to continue while in rehabilitation and beyond. This highlights the importance of thorough medication reconciliation by the referring physician so that unnecessary medications are discontinued before patient transfer to another treating facility. Another possibility is that the medication guideline recommendations were overlooked by the rehabilitation physician. However, it should be noted that there are clinical situations when the rehabilitation physician may need to continue the patient on AEDs (eg, penetrating TBI) or at the preference of the patient's neurosurgeon. It is important that all physicians treating TBI patients in acute and rehabilitation settings receive appropriate AED education and communicate regarding ongoing AED need to improve consistency with practice guidelines. Measures can be taken to increase compliance with guidelines, including in-service lectures or auto stop functions on electronic ordering sets.[8]

Although our results indicate that phenytoin was the most commonly used drug for seizure prophylaxis, levetiracetam has since become a popular alternative due to the ease of dosing and lack of required monitoring.[9] Many patients were found to be taking AEDs for reasons other than seizure prophylaxis. For example, 48 (27.75%) of the total 173 patients were prescribed valproic acid for management of agitation or for mood stabilization during their acute care hospitalization. This is not surprising, as psychotropic medications are used in the management of problematic behaviors that can often follow TBI. Our sample also showed that 38 (21.97%) of 173 patients were continued on valproic acid during their inpatient rehabilitation stay for behavioral or mood management.

Interestingly, 96 (55.49%) of the 173 patients included were never started on seizure prophylaxis. These 96 patients were similar to the "overutilization" and "other utilization" groups in terms of severity of injury (see Table 1). This suggests a lack of uniformity in the initiation of seizure prophylaxis upon hospital presentation following TBI. While identifying the reasons for this variation was not an aim of this study, the finding does highlight the need for a better clinical algorithm to identify patients who would benefit from seizure prophylaxis following their TBI.

In addition to the negative side effects of medication overuse, overutilization of resources remains a growing concern for healthcare consumers and providers due to escalating costs and more restricted access to care.[12] In an effort to promote judicious medical decision making as supported by medical evidence, the American Board of Internal Medicine Foundation has developed

the *Choosing Wisely* campaign.[13] The campaign aims to enable physicians to promote more effective use of healthcare resources, be better stewards of finite healthcare resources,[12] and seek evidence-based recommendations for their patients to make wise decisions that avoid unnecessary tests and treatments. This initiative has expanded to 60 specialty physician groups (eg, American Academy of Neurology, American Academy of Family Physicians, and American College of Physicians) that have formulated lists of "Things Providers and Patients Should Question." Such lists include evidence-based recommendations to guide reasonable and necessary choices regarding patient care. Recently, the AAPM&R was added to the *Choosing Wisely* campaign with guidelines for the management of low back pain released in September 2014. The campaign has yet to expand to other aspects of rehabilitation medicine such as TBI because the field lacks clear evidence-based guidelines and treatments are often based on best clinical knowledge and case studies. In the realm of seizure prophylaxis following TBI, however, the research has been deemed strong for the past 20 years,[3] suggesting that the recommendations should be followed closely with little clinical variance.

It is important to note that this study has a number of major limitations including the small sample size, retrospective design, and the fact that data represent only 1 hospital within the TBIMS. When first designing the study, we hoped to examine predictors of overutilization (eg, age, gender, severity of injury), but our sample size was too small to draw significant predictions for overutilization or determine trends in AED usage across time. Another limitation was that we only included patients who were enrolled in the TBIMS. More than half of patients with TBI admitted to our inpatient rehabilitation unit annually are not enrolled into the TBIMS database, as they do not admit from level 1 trauma centers with Model Systems qualifications. If we had instead included all patients with a diagnosis of TBI, regardless of acute care hospitalization location, we suspect based on clinical observation that our overutilization rate would have been much higher. Finally, rates of overutilization and failure to stop may vary considerably across TBIMS centers and other acute hospitals treating TBI patients. As a result, the ability to make inferences outside of our system is limited.

CONCLUSION

It is important to comply with seizure prophylaxis guidelines in patients after TBI because no evidence exists for AED efficacy beyond 7 days in reducing PTS rate. Furthermore, AEDs can create neurobehavioral and cognitive impairments beyond those caused by the underlying brain injury. It is important that clinicians treating patients in the acute and rehabilitation settings receive appropriate AED education and communicate their reasons for ongoing AEDs to improve consistency with practice guidelines. Measures can be taken to increase compliance with guidelines including education intervention with in-service lectures and auto stop functions on electronic ordering sets. Improved compliance with these guidelines can decrease potential patient side effects, lower healthcare costs, and reduce overutilization of healthcare resources.

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