# Prevalence of Early Posttraumatic Seizures in Children With Moderate to Severe Traumatic Brain Injury Despite Levetiracetam Prophylaxis*

Melissa G. Chung, MD[1,2]; Nicole F. O'Brien, MD[1]

**Objectives:** To evaluate the prevalence of early seizures after levetiracetam prophylaxis in children with moderate to severe traumatic brain injury.

**Design:** Prospective observational study.

**Setting:** Level 1 pediatric trauma center.

**Patients:** We enrolled 34 patients between the ages of 0–18 years with moderate to severe traumatic brain injury admitted to the PICU at a level 1 trauma center who received levetiracetam for early posttraumatic seizure prophylaxis.

**Measurements and Main Results:** Primary outcome was the prevalence of early posttraumatic seizures that were defined as clinical seizures within 7 days of injury. In 6 of 34 patients (17%), clinical seizures developed despite levetiracetam prophylaxis. An additional two patients had nonconvulsive seizures. This prevalence is similar to that reported in the literature in this patient population who do not receive seizure prophylaxis (20–53%) and is higher than that in patients who receive phenytoin prophylaxis (2–15%). Patients with early posttraumatic seizures were younger (median age, 4 mo) ($p < 0.001$) and more likely to have suffered from abusive head trauma ($p < 0.0004$).

**Conclusions:** Early clinical posttraumatic seizures occurred frequently in children with moderate to severe traumatic brain injury despite seizure prophylaxis with levetiracetam. Younger children and those with abusive head trauma were at increased risk of seizures. Further studies are needed to evaluate the efficacy of levetiracetam before it is routinely used for seizure prophylaxis in these children, particularly in young children and those who have suffered from abusive head trauma. (*Pediatr Crit Care Med* 2016; 17:150–156)

**Key Words:** antiepileptics; children; head injury; levetiracetam seizures; traumatic brain injury

Traumatic brain injury (TBI) is a leading cause of childhood morbidity and mortality. An estimated 475,000 children who are less than 14 years old sustain traumatic brain injuries each year in the United States (1, 2). Over 50,000 children are hospitalized each year and account for more than $1 billion dollars in healthcare costs in the United States alone (3, 4). Mortality is high, and TBI is the leading cause of death in children between the ages of 1–18 in developed countries (1).

Patients with moderate to severe TBI are at high risk of early posttraumatic seizures (EPTS), and young children seem to be at the highest risk (5–7). EPTS are defined as seizures that occur within the first 7 days of injury. Seizures may contribute to secondary injury by increasing metabolic demand, inducing hypoxia, and elevating intracranial pressure (ICP).

Studies in adults have shown that phenytoin prophylaxis effectively reduces the prevalence of EPTS (8, 9). Phenytoin is processed in the liver via the p450 system; so, it may have significant interactions with other medications. It also may cause hypotension (primarily with rapid infusion), dizziness, somnolence, and ataxia, especially at higher doses. Rarely, it also may cause hepatotoxicity, arrhythmias, or cytopenias. A randomized, double-blinded, placebo-controlled trial by Temkin et al (8) found that prophylaxis with phenytoin reduced the prevalence of EPTS in adults from 14.2% to 3.5% ($p < 0.001$). Less data are available in children but still suggest that phenytoin may help prevent early seizures (6). A retrospective study by Lewis et al (6) found that 53% of children with severe TBI had EPTS without antiepileptic drugs (AED) prophylaxis, whereas only in 15% of the children treated with phenytoin, EPTS developed. Current guidelines for severe TBI management in children recommend phenytoin be considered for early seizure prophylaxis (10).

However, since the approval of the IV formulation of levetiracetam by the Federal Food and Drug Administration in 2007, levetiracetam has been increasingly used instead of phenytoin

*See also p. 173.

[1]Division of Critical Care Medicine, Department of Pediatrics, Nationwide Children's Hospital, the Ohio State University, Columbus, OH.

[2]Section of Neurology, Department of Pediatrics, Nationwide Children's Hospital, The Ohio State University, Columbus, OH.

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Address requests for reprints to: Melissa G. Chung, MD, Section of Neurology, 700 Children's Dr., Columbus, OH 43205.



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for early seizure prophylaxis (11). Levetiracetam is a nonenzyme–inducing antiepileptic drug with a better side-effect profile. It does not have significant drug-drug interactions. Levetiracetam does not tend to cause hypotension but may still cause somnolence, dizziness, irritability, and behavioral problems. Levetiracetam also rarely has been reported to cause hepatotoxicity and cytopenias. In addition, levetiracetam does not require drug level monitoring.

However, the efficacy of levetiracetam in preventing EPTS in children with TBI has not been described. Therefore, we developed this prospective, observational trial to evaluate the prevalence of EPTS in children receiving levetiracetam prophylaxis following moderate to severe TBI.

## MATERIALS AND METHODS

We performed a prospective, observational study at Nationwide Children's Hospital in Columbus, OH, which is a pediatric level 1 trauma center. Patients between the ages of 0–18 years admitted to the PICU from 2011 to 2014 with moderate to severe TBI who received levetiracetam were included. Moderate to severe TBI was defined as postresuscitation Glasgow Coma Scale (GCS) or modified pediatric GCS score up to 12 (12). Patients who were begun on levetiracetam only after a seizure already had occurred were excluded from the study. We also excluded patients who had a preexisting history of seizures/epilepsy.

Demographic information, including age, gender, race, cause of injury, and neuroimaging results, was recorded. The prevalence and treatment of EPTS (defined as clinical seizures that occurred within 7 d of injury) were noted. Seizure prophylaxis strategy and electroencephalographic monitoring were left to the discretion of the treatment team.

All patients received routine ICU care. Patients with moderate TBI underwent frequent neurologic checks. Patients with severe TBI were treated following the Society of Critical Care Medicine guidelines (10). Children with mass lesions underwent primary decompressive craniotomy with resection of the mass lesion at the discretion of the neurosurgical attending physician. Other care included tracheal intubation, elevation of the head of the bed to 30 degrees, and placement of an ICP monitor. Ventriculostomy was placed when technically feasible at the discretion of the neurosurgical attending physician. Subsequent cerebrospinal fluid drainage was taken if ventriculostomy was present. If ventriculostomy could not be inserted, an intraparenchymal monitor was placed (Camino or Licox, Integra Neurosciences, Plainsboro, NJ). Electroencephalographic monitoring is not part of the standard treatment protocol for patients with TBI in our ICU. Patients who receive electroencephalographic monitoring are typically undergoing neuromuscular blockade or have clinical findings concerning for seizures that trigger the placement of electroencephalographic leads.

Using combinations of the key words seizures, early posttraumatic seizures, early seizures, children, pediatric, TBI, head injury, antiepileptic, phenytoin, and levetiracetam, a literature review using MEDLINE was done to identify articles that previously have studied EPTS in children with moderate to severe TBI. Articles were reviewed for historical data on the prevalence of clinical EPTS in children with and without seizure prophylaxis after moderate to severe TBI.

Statistical analysis was performed using GraphPad Prism software (GraphPad Software, Inc, La Jolla, CA). Descriptive statistics were calculated for all dichotomous and categorical variables, and medians were calculated for continuous variables. Nonparametric *t* tests were used to compare the age, GCS score in first 24 hours, the presence of abusive head trauma (AHT) or non-AHT, dosage of prophylactic levetiracetam in patients, and other treatment interventions in patients in whom EPTS developed and in whom EPTS did not.

This study was approved by the Nationwide Children's Hospital Institutional Review Board.

## RESULTS

A total of 69 patients with moderate to severe TBI without a history of prior seizures were identified. Twenty-one patients were excluded because they did not receive any seizure prophylaxis. Twelve patients were excluded because of the occurrence of seizures before initiation of antiepileptics. Two patients were excluded because they received phenytoin instead of levetiracetam for seizure prophylaxis. Thirty-four patients received levetiracetam for seizure prophylaxis and were included in the study analysis.

### Baseline Demographics

Seventy-eight percent of patients were men. Fifty-nine percent of patients were Caucasian. The median age was 6 years (range, 5 d to 16 yr). The median initial GCS score was 8 (range, 3–12). Patients received 5–40 mg/kg/d of levetiracetam for prophylaxis (median, 20 mg/kg/d). Electroencephalography (EEG)

**TABLE 1. Mechanism of Injury and Marshall Computed Tomographic Scores for Patients**

| Patient Characteristic | Patients (%) |
|---|---|
| Marshall computed tomographic score | |
| 1 | 0 |
| 2 | 6 (17.6) |
| 3 | 12 (35.3) |
| 4 | 1 (2.9) |
| 5 | 6 (17.6) |
| 6 | 9 (26.5) |
| Mechanism of injury | |
| Fall | 7 (20.5) |
| Motor vehicle accident | 8 (23.5) |
| Pedestrian vs auto | 8 (23.5) |
| Abusive head trauma | 7 (20.5) |
| Other | 4 11.8) |

was done in 15 patients. Eight EEGs were performed due to intracranial hypertension requiring neuromuscular blockade, and seven were done due to clinical concerns for seizures. Further demographics are given in **Table 1** (32).

### Prevalence of Seizures

Clinical seizures developed in 6 of 34 children (17.6%) despite prophylactic levetiracetam. One patient had only convulsive seizures, and five patients had both convulsive and nonconvulsive seizures. Seizures began on either day 2 or 3 after injury in all patients who seized (of note, the patients who had seizures in the field or in the emergency department prior to receiving levetiracetam are not included in this study). Clinical details of patients with EPTS are given in **Tables 2** and **3**. Patients in whom EPTS developed were younger than those in whom seizures did not develop (median age, 4 mo versus 10 yr) ($p < 0.0001$) and were more likely to have suffered AHT ($p = 0.0004$). There was no difference in the initial dose of levetiracetam that patients with clinical seizures received (median, 20 mg/kg/d; range, 5–40 mg/kg/d) when compared with patients who did not have clinical seizures (median, 20 mg/kg/d; range, 10–40 mg/kg/d) ($p = 0.87$). The initial GCS score for patients with seizures was slightly higher (median, 9) than that for patients without seizures (median, 7) ($p = 0.04$). Eighty-three percent of the patients with early clinical posttraumatic seizures required at least one additional AED for seizure control.

This prevalence of early clinical posttraumatic seizures is slightly lower than that reported in the literature in children with TBI who do not receive seizure prophylaxis (20–53%) and is higher than the rate seen in children treated with phenytoin (2–15%) (**Fig. 1**).

## DISCUSSION

EPTS occurred frequently in children with moderate to severe TBI despite prophylaxis with levetiracetam and tended to happen more often in younger patients and those who suffered AHT.

To our knowledge, this is the first study to look at the prevalence of EPTS in children on levetiracetam for seizure prophylaxis after moderate to severe TBI. A recent study by Pearl et al (13) reported on the safety and feasibility data of the use of levetiracetam to reduce the occurrence of EPTS. However, the article restricted its pediatric inclusion criteria to children who are 6–17 years old at risk of posttraumatic epilepsy, defined as intracranial hemorrhage or penetrating injury, depressed skull fracture with subdural hemorrhage, or EPTS. Our study included children with a diagnosis of TBI only and included a broader age range. Thus, the study by Pearl et al (13) addressed a different objective than the one explored in our study.

Our results suggest that levetiracetam is not more effective than phenytoin and possibly not as effective based on historical controls. The percentage of patients (17.6%) in our study in whom early clinical posttraumatic seizures developed while on levetiracetam is similar to that described in prior studies in which patients did not receive any seizure prophylaxis. Two prior studies have reported on

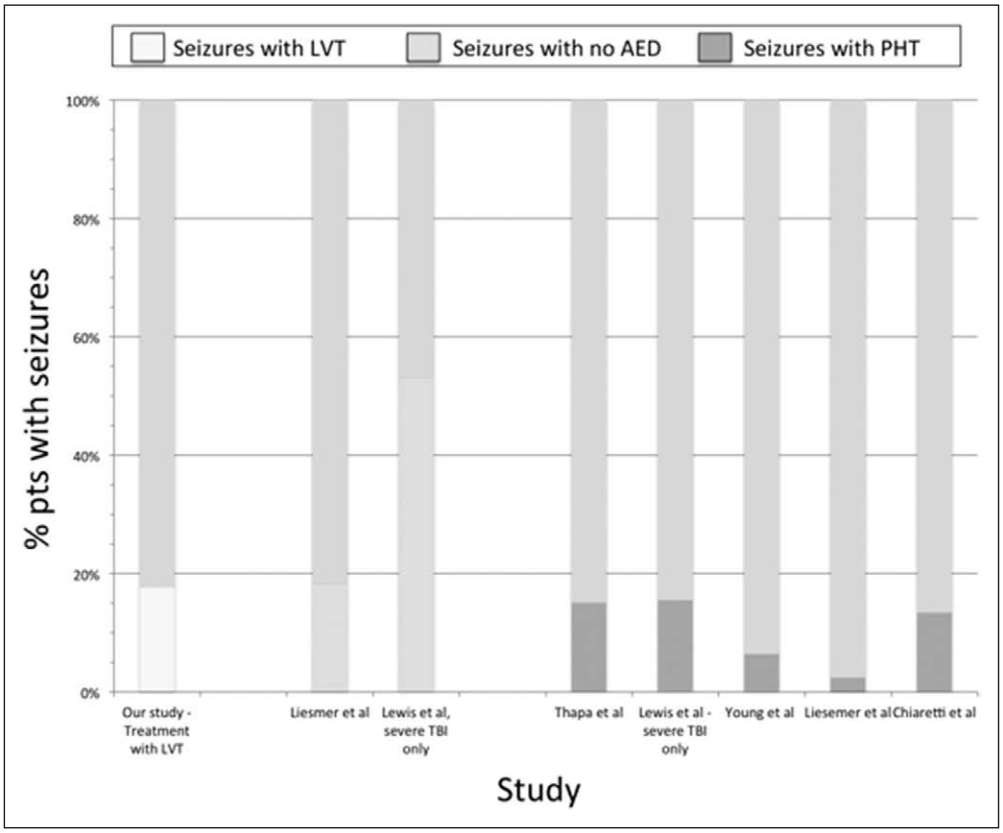


**Figure 1.** Prevalence of clinical early posttraumatic seizures in children treated with levetiracetam (LVT), phenytoin, or without any prophylaxis in our study and historical studies. The prevalence of clinical seizures despite treatment with LVT in our study (17%) is similar to that reported in children with traumatic brain injury (TBI) who do not receive seizure prophylaxis (20–53%) and is slightly higher than the rate seen in children treated with phenytoin (2–15%). All studies used for comparison defined early posttraumatic seizures (EPTS) as clinical seizures only that occurred in the first 7 days after injury. The studies by Lewis et al (6), Liesemer et al (7), and Young et al (18) are further described in the text of the discussion. The study by Thapa et al (17) was a prospective observational study of patients (adult and pediatric) in India with Glasgow Coma Scale (GCS) scores between 4 and 15. Patients with GCS scores up to 4 were excluded. All patients with GCS scores less than 13 were treated with phenytoin. The pediatric data only are included in the figure. The study by Chiaretti et al (25) is a retrospective study of 122 children admitted with severe TBI to a tertiary-care PICU that was designed to look at prognostic factors and outcome in children with severe TBI. The occurrence of EPTS was one of the factors evaluated in the article. AED = antiepileptic drugs, PHT = phenytoin.

**TABLE 2. Comparison of Clinical Information for Patients With Clinical Seizures and Without Seizures**

| Patient Characteristic | Patients With Seizures (%) | Patients Without Seizures (%) | *p* |
|---|---|---|---|
| Age (median range) | 4 mo (1–20 mo) | 10 yr (4 mo to 15.7 yr) | < 0.0001 |
| Glasgow Coma Scale score | 9 (7–12) | 7 (3–12) | 0.04 |
| Levetiracetam dose (mg/kg/d) | 20 (5–20) | 20 (10–40) | 0.52 |
| Mechanism of injury—abusive head trauma | 6/6 patients (100) | 2/28 (7) | 0.0004 |
| Maximum pilot score (median range) | 6.5 (1–12) | 7 (1–30) | 0.70 |
| Intubated | 5/6 (83) | 24/28 (86) | 1 |
| ICP monitor | 1/6 (17) | 14/28 (50) | 0.2 |
| Extraventricular drain | 1/6 (17) | 6/28 (21) | |
| Intraparenchymal monitor | 0/6 | 8/28 (29) | |
| Elevated ICP monitor (of those tested) | 0/1 (0) | 11/14 (79) | 1 |
| Hypoxia pre-ICU | 0/6 (0) | 3/28 (11) | 1 |
| Hypoxia in ICU | 0/6 (0) | 2/28 (0.07) | 1 |
| Hypotension pre-ICU | 1/6 (17) | 4/28 (14) | 1 |
| Hypotension in ICU | 0/6 (0) | 3/28 (11) | 1 |
| Febrile in first 7 d | 4/6 (67) | 16/28 (57) | 1 |
| Nadir sodium level in first 7 d (median range) | 135 (129–139) | 136 (124–151) | 0.4 |
| Craniotomy | 1/6 (17) | 11/28 (39) | 0.39 |
| Neuromuscular blockade | 0/6 (0) | 8/28 (29) | 0.3 |
| Hypertonic saline | 1/6 (17) | 15/28 (54) | 0.18 |

ICP = intracranial pressure.

the prevalence of clinical seizures without AED prophylaxis in children. A retrospective observational study of children with moderate to severe TBI by Liesemer et al (7) found that in 26 of 142 (18.3%) patients who did not receive AED prophylaxis, seizures developed. Another retrospective study by Lewis et al (6) of children between 3 months and 15 years old reported a prevalence of EPTS without AED prophylaxis in 52.3% of patients with severe TBI. This value is higher than that seen our study but likely is related to the fact that our study included patients with moderate TBI as well as severe TBI (6). Given that the majority of our patients did not undergo long-term electroencephalographic monitoring, the percentage of patients with seizures on levetiracetam actually may be underestimated in our study if nonconvulsive seizures are taken into account. Several studies have reported that subclinical seizures are common in children with TBI especially younger children or AHT (14–16).

A direct comparison between phenytoin and levetiracetam cannot be made in this study since it was an observational pilot study. Also, we found that very few patients (and primarily those with immediate seizures) received phenytoin during this study period. However, the prevalence of seizures in our group of 17.6% is higher than that reported in children that received phenytoin prophylaxis in historical studies. Two retrospective studies that collected data prior to the introduction of IV levetiracetam reported a prevalence of clinical EPTS of 9.3% and 15% in children treated with phenytoin (7, 17). In the study Lewis et al (6), phenytoin prophylaxis decreased the occurrence of clinical seizures in children with severe TBI from 52.3% to 9.3% ($p = 0.04$). This study remains the basis for why phenytoin specifically is recommended for consideration for seizure prophylaxis in children with severe TBI in the current pediatric management guidelines (10). In contrast to the study by Lewis et al (6), a randomized control study of patients who are less than 16 years old with moderate to severe TBI by Young et al (18) concluded that phenytoin prophylaxis did not decrease the occurrence of EPTS. Seven percent of patients in the phenytoin group had seizures, but only 5% in the placebo group experienced them. However, the generalizability of this study is limited as patients were only followed up for 48 hours after injury, and only two thirds of patients were monitored for even that duration. Thus, the true prevalence of EPTS in the study by Young et al (18) may have been underestimated because patients were not followed up for a full 7 days. Overall, based on the above studies, current data including that from our

**TABLE 3. Clinical Information for Patients With Early Posttraumatic Seizures**

| Age (mo) | Sex | Mechanism of Injury | Glasgow Coma Scale Score | Neuroimaging Findings | Marshall Computed Tomographic Scale | Dose of LVT (mg/kg/d) | Type of Seizures | Antiepileptic Drugs Needed |
|---|---|---|---|---|---|---|---|---|
| 1.5 | M | AHT | 10 | L parietal skull fracture, L SDH with shift, and R frontal and temporal contusions | 6 | 20 | C and NC | LVT |
| 8.5 | M | AHT | 9 | Chronic SDH, acute R SDH, and R cerebral ischemia | 6 | 20 | C and NC | LVT and PB |
| 4 | M | AHT | 8 | Bilateral SDH, R frontal IPH, and hypoxic-ischemic encephalopathy | 2 | 5 | C and NC | LVT, PHT, PB, and midazolam drip |
| 20.5 | F | AHT | 12 | R SDH, diffuse edema, R cerebral ischemia, watershed infarcts, and L anterolateral ischemia | 3 | 20 | C and NC | LVT, PHT, and midazolam drip |
| 4 | M | AHT | 12 | R frontoparietal SDH with mass effect and R frontal lobe ischemia | 6 | 20 | C | LVT and PHT |
| 4 | M | AHT | 7 | Chronic SDH, acute SDH, SAH, multiple cerebral contusions, watershed infarcts, and HIE | 3 | 20 | C and NC | LVT, PHT, and midazolam drip |

M = male, F = female, AHT = abusive head trauma, L = left, SDH = subdural hematoma, R = right, C = convulsive, NC = nonconvulsive, LVT = levetiracetam, PB = phenobarbital, IPH = intraparenchymal hemorrhage, PHT = phenytoin, SAH = subarachnoid hemorrhage.

study do not seem to suggest that levetiracetam is superior to and may be inferior to phenytoin in preventing EPTS in children with moderate to severe TBI.

The suggestion that levetiracetam is not superior to phenytoin in children is similar to the adult literature on levetiracetam prophylaxis after TBI. In retrospective studies, the prevalence of EPTS was similar in patients who received levetiracetam compared with patients who received phenytoin (19, 20). Two prospective studies also concluded that there was no difference in the efficacy of levetiracetam versus phenytoin (21, 22). A recent metaanalysis of adult studies concluded that levetiracetam is not superior to phenytoin for seizure prophylaxis in adults with brain injury, including but not limited to trauma patients (23).

Some authors have argued that with the lack of superiority between the two drugs, levetiracetam may be the better choice because of a more benign side-effect profile and lack of need for monitoring drug levels. However, levetiracetam is a much more expensive medication and thus less cost-effective. A recent cost analysis found that a 7-day course of levetiracetam was more than 10 times more expensive than prophylaxis with fosphenytoin or phenytoin, including drug monitoring levels (24). The cost-effectiveness ratio for phenytoin was 1.58/quality-adjusted life years versus 20.72/quality-adjusted life years for levetiracetam.

It also is concerning that the prevalence of seizures with levetiracetam prophylaxis is higher than that reported with phenytoin prophylaxis in the literature as EPTS correlates with a worse outcome in children with severe TBI. A retrospective study of 122 children with severe TBI found that EPTS were associated with worse Glasgow Outcome Scale scores 6 months later (25). Children with AHT who in our study were at increased risk of developing EPTS have been reported to have an odds ratio of 4.56 of a poor outcome if they suffered early seizures (26, 27). Seizures may contribute poor outcome by increasing excitotoxicity, causing further cerebral ischemia,

and increasing ICP, all which can lead to secondary injury (28–30). A retrospective review of 130 children with severe TBI also found that EPTS significantly increased children's risk of late posttraumatic seizures (31). Thus, if levetiracetam fails to adequately prevent EPTS, then caution should be used before this drug is routinely substituted for phenytoin, as such actions may be costly, both monetarily and in regards to long-term morbidity.

Our results also found that the children in whom EPTS developed were significantly younger and more likely to have AHT. The finding that younger children are at higher risk for seizures is consistent with prior studies (5–7, 31). Several studies have reported that AHT carries a high risk of EPTS (14, 15, 27). AHT may represent a unique subpopulation of children with TBI given that children are at risk of diffuse injury from rotation forces and also may have suffered repeated episodes of trauma rather than a single insult. The prevalence of seizures in these children may be higher regardless of the AED used for prophylaxis, whether it be phenytoin or levetiracetam.

Because this study was a prospective, observational trial, the results are limited by the small sample size. The dosage of levetiracetam also was dictated by the treatment team. It is possible that the drug may be more effective at higher doses or after a loading dose. The data from this preliminary study though support the need for a larger randomized study with regulated dosing of levetiracetam and patients received electroencephalographic monitoring to explore the utility of levetiracetam for EPTS prophylaxis in children with TBI particularly in young children and those who have suffered from abusive head trauma.

## CONCLUSIONS

EPTS still occurred in 17.6% of children with moderate to severe TBI despite levetiracetam prophylaxis. Further studies are required to evaluate the efficacy of this drug, before it is routinely used for seizure prophylaxis in these children, particularly in young children and those who have suffered from abusive head trauma.

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## REFERENCES

1. Centers for Disease Control and Prevention: Web-Based Injury Statistics Query and Reporting System. 2010. Available at: http://www.cdc.gov/ncipc/wisqars/. Accessed January 1, 2014
2. Centers for Disease Control and Prevention (CDC). CDC grand rounds: Reducing severe traumatic brain injury in the United States. *MMWR Morb Mortal Wkly Rep* 2013; 62:549–552
3. Shi J, Xiang H, Wheeler K, et al: Costs, mortality likelihood and outcomes of hospitalized US children with traumatic brain injuries. *Brain Inj* 2009; 23:602–611
4. Schneier AJ, Shields BJ, Hostetler SG, et al: Incidence of pediatric traumatic brain injury and associated hospital resource utilization in the United States. *Pediatrics* 2006; 118:483–492
5. Asikainen I, Kaste M, Sarna S: Early and late posttraumatic seizures in traumatic brain injury rehabilitation patients: Brain injury factors causing late seizures and influence of seizures on long-term outcome. *Epilepsia* 1999; 40:584–589
6. Lewis RJ, Yee L, Inkelis SH, et al: Clinical predictors of post-traumatic seizures in children with head trauma. *Ann Emerg Med* 1993; 22:1114–1118
7. Liesemer K, Bratton SL, Zebrack CM, et al: Early post-traumatic seizures in moderate to severe pediatric traumatic brain injury: Rates, risk factors, and clinical features. *J Neurotrauma* 2011; 28:755–762
8. Temkin NR, Dikmen SS, Wilensky AJ, et al: A randomized, double-blind study of phenytoin for the prevention of post-traumatic seizures. *N Engl J Med* 1990; 323:497–502
9. Wohns RN, Wyler AR: Prophylactic phenytoin in severe head injuries. *J Neurosurg* 1979; 51:507–509
10. Kochanek PM, Carney N, Adelson PD, et al; American Academy of Pediatrics-Section on Neurological Surgery; American Association of Neurological Surgeons/Congress of Neurological Surgeons; Child Neurology Society; European Society of Pediatric and Neonatal Intensive Care; Neurocritical Care Society; Pediatric Neurocritical Care Research Group; Society of Critical Care Medicine; Paediatric Intensive Care Society UK; Society for Neuroscience in Anesthesiology and Critical Care; World Federation of Pediatric Intensive and Critical Care Societies: Guidelines for the acute medical management of severe traumatic brain injury in infants, children, and adolescents–second edition. *Pediatr Crit Care Med* 2012; 13(Suppl 1):S1–82
11. Kruer RM, Harris LH, Goodwin H, et al: Changing trends in the use of seizure prophylaxis after traumatic brain injury: A shift from phenytoin to levetiracetam. *J Crit Care* 2013; 28:883.e9–883.e13
12. Teasdale G, Jennett B: Assessment of coma and impaired consciousness. A practical scale. *Lancet* 1974; 2:81–84
13. Pearl PL, McCarter R, McGavin CL, et al: Results of phase II levetiracetam trial following acute head injury in children at risk for post-traumatic epilepsy. *Epilepsia* 2013; 54:e135–e137
14. Arndt DH, Lerner JT, Matsumoto JH, et al: Subclinical early posttraumatic seizures detected by continuous EEG monitoring in a consecutive pediatric cohort. *Epilepsia* 2013; 54:1780–1788
15. Goldstein JL, Leonhardt D, Kmytyuk N, et al: Abnormal neuroimaging is associated with early in-hospital seizures in pediatric abusive head trauma. *Neurocrit Care* 2011; 15:63–69
16. Hasbani DM, Topjian AA, Friess SH, et al: Nonconvulsive electrographic seizures are common in children with abusive head trauma*. *Pediatr Crit Care Med* 2013; 14:709–715
17. Thapa A, Chandra SP, Sinha S, et al: Post-traumatic seizures-A prospective study from a tertiary level trauma center in a developing country. *Seizure* 2010; 19:211–216
18. Young KD, Okada PJ, Sokolove PE, et al: A randomized, double-blinded, placebo-controlled trial of phenytoin for the prevention of early posttraumatic seizures in children with moderate to severe blunt head injury. *Ann Emerg Med* 2004; 43:435–446
19. Caballero GC, Hughes DW, Maxwell PR, et al: Retrospective analysis of levetiracetam compared to phenytoin for seizure prophylaxis in adults with traumatic brain injury. *Hosp Pharm* 2013; 48:757–761
20. Jones KE, Puccio AM, Harshman KJ, et al: Levetiracetam versus phenytoin for seizure prophylaxis in severe traumatic brain injury. *Neurosurg Focus* 2008; 25:E3
21. Inaba K, Menaker J, Branco BC, et al: A prospective multicenter comparison of levetiracetam versus phenytoin for early post-traumatic seizure prophylaxis. *J Trauma Acute Care Surg* 2013; 74:766–771
22. Szaflarski JP, Sangha KS, Lindsell CJ, et al: Prospective, randomized, single-blinded comparative trial of intravenous levetiracetam versus phenytoin for seizure prophylaxis. *Neurocrit Care* 2010; 12:165–172
23. Zafar SN, Khan AA, Ghauri AA, et al: Phenytoin versus Leviteracetam for seizure prophylaxis after brain injury - A meta analysis. *BMC Neurol* 2012; 12:30

24. Cotton BA, Kao LS, Kozar R, et al: Cost-utility analysis of levetiracetam and phenytoin for posttraumatic seizure prophylaxis. *J Trauma* 2011; 71:375–379
25. Chiaretti A, Piastra M, Pulitanò S, et al: Prognostic factors and outcome of children with severe head injury: An 8-year experience. *Childs Nerv Syst* 2002; 18:129–136
26. Rhine T, Wade SL, Makoroff KL, et al: Clinical predictors of outcome following inflicted traumatic brain injury in children. *J Trauma Acute Care Surg* 2012; 73:S248–S253
27. Greiner MV, Lawrence AP, Horn P, et al: Early clinical indicators of developmental outcome in abusive head trauma. *Childs Nerv Syst* 2012; 28:889–896
28. Vespa P, Prins M, Ronne-Engstrom E, et al: Increase in extracellular glutamate caused by reduced cerebral perfusion pressure and seizures after human traumatic brain injury: A microdialysis study. *J Neurosurg* 1998; 89:971–982
29. Posner JB, Plum F, Van Poznak A: Cerebral metabolism during electrically induced seizures in man. *Arch Neurol* 1969; 20:388–395
30. Knoblich OE, Gaab M, Weber W, et al: Intracranial pressure and electrical activity of the brain in various forms of experimental and clinical seizures. *Neurosurg Rev* 1980; 3:243–249
31. Arango JI, Deibert CP, Brown D, et al: Posttraumatic seizures in children with severe traumatic brain injury. *Childs Nerv Syst* 2012; 28:1925–1929
32. Marshall LF, Marshall SB, Klauber MR, et al: The diagnosis of head injury requires a classification based on computed axial tomography. *J Neurotrauma* 1992; 9(Suppl 1):S287–S292