

Clinical Approach to Posttraumatic Epilepsy

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Abstract

Traumatic brain injury (TBI) is one of the most common causes of acquired epilepsy, and posttraumatic epilepsy (PTE) results in significant somatic and psychosocial morbidity. The risk of developing PTE relates directly to TBI severity, but the latency to first seizure can be decades after the inciting trauma. Given this “silent period,” much work has focused on identification of molecular and radiographic biomarkers for risk stratification and on development of therapies to prevent epileptogenesis. Clinical management requires vigilant neurologic surveillance and recognition of the heterogeneous endophenotypes associated with PTE. Appropriate treatment of patients who have or are at risk for seizures varies as a function of time after TBI, and the clinician’s armamentarium includes an ever-expanding diversity of pharmacological and surgical options. Most recently, neuromodulation with implantable devices has emerged as a promising therapeutic strategy for some patients with refractory PTE. Here, we review the epidemiology, diagnostic considerations, and treatment options for PTE and develop a roadmap for providers encountering this challenging clinical entity.

Keywords

- ▶ traumatic brain injury
- ▶ epilepsy
- ▶ posttraumatic epilepsy
- ▶ seizure
- ▶ neuromodulation

“...the brain may be injured by contusion, laceration, compression, and it is well known that these insults may result in epilepsy after a silent period of strange ripening. That period lasts for months or years, but these insults produce epilepsy in the case of one individual and not in the case of another.” --W. Penfield (1961)¹

The association between epilepsy and head injury has been known since antiquity,^{2,3} but the societal impact of this connection has never been greater. Traumatic brain injury (TBI) accounts for 2.5 million emergency department (ED) visits, more than 280,000 hospitalizations, and 50,000 deaths in the United States each year.⁴ Incidence estimates are staggering—rates of TBI-related ED visits have increased 70% over the past decade,⁴ and a TBI now occurs every 21 seconds^{5,6}—but these figures are likely conservative because many milder cases go unrecognized, leading to the term “silent epidemic.”^{7,8} Epilepsy, the enduring tendency for recurrent, unprovoked seizures,⁹ is among the most common neurologic disorders¹⁰ and frequently develops in

the wake of TBI. Posttraumatic epilepsy (PTE) accounts for 5 to 6% of all epilepsy,^{11–13} including up to 20% of acquired forms.¹¹ Posttraumatic epilepsy is the most common cause of new-onset epilepsy in young adults, and following penetrating brain wounds, the likelihood of developing epilepsy is as high as 53%.^{2,14} Indeed, the relative risk of epilepsy after severe TBI is exceeded only by subarachnoid hemorrhage and brain tumor.¹⁵ With the global proliferation in firearms¹⁶ and the identification of military blast exposure as the “signature injury” of recent warfare,^{17–19} rates of TBI and PTE will likely continue to increase in the future.

Although often neglected as an outcome measure in TBI studies,²⁰ PTE is the source of considerable somatic and psychosocial morbidity²¹ and will be encountered by general neurologists and primary care physicians alike. Proper management of PTE requires an understanding of the risk factors, natural history, clinical heterogeneity, and treatment options. Here, we review these topics with a focus on clinical approach to PTE. The underlying pathophysiology of PTE and other

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neurologic syndromes related to TBI are reviewed elsewhere in this issue.

Definitions and Risk Factors

A seizure that occurs after head trauma can be described by the time interval between these events. Although definitions vary, many researchers adopt the following²: (1) immediate seizures, which occur less than 24 hours after injury; (2) early seizures, which occur between 24 hours and one week after injury; and (3) late seizures, which occur more than a week after injury. Posttraumatic epilepsy is operationally defined as the occurrence of one or more unprovoked late seizures after TBI.

In both civilian and military populations, the risk of developing PTE depends heavily on the severity of the inciting injury.^{19,22–24} The nosology of TBI severity is not universal, but a widely used classification is that of Annegers and colleagues²⁵: (1) Mild TBI, which connotes loss of consciousness for less than 30 minutes and no skull fracture; (2) moderate TBI, with loss of consciousness 30 minutes to 24 hours, with or without skull fracture; and (3) severe TBI, involving loss of consciousness greater than 24 hours, with brain contusion, intracranial hematoma, or skull fracture. Compared with the general population, the relative risks of developing epilepsy after mild, moderate, and severe TBI are 1.5, 2.9, and 17, respectively.²⁴ Consistent with a critical role for injury severity, multivariate analyses indicate that risk factors for PTE include penetrating injuries, multiple contusions, intracranial hemorrhage, and neurosurgical procedures.^{24,26–29} A practical implication of these observations is that it is essential to collect as much information as possible about the nature of a patient's prior head trauma for the purposes of risk stratification.

The issue of whether early posttraumatic seizures predict late seizures (i.e., PTE) has been given much attention, but results are conflicting. Risk factors for early and late seizures are similar, and a large, population-based cohort study found that early seizures were not an independent risk factor for late seizures.²⁴ This suggests that late seizures follow early posttraumatic seizures no more often than they do a first unprovoked seizure in the general population.^{30,31} However, other studies have found that early seizures do increase the risk of PTE,^{22,26,32–34} and the matter remains controversial. There is more agreement, however, that a first late seizure has a high risk of recurrence, 47% after 1 month and 86% within 2 years in one study.³⁵ Treatment implications in the context of these data are discussed below.

Other risk factors for PTE have emerged recently, including depression and multiple comorbid medical conditions.²² Hereditary predisposition to PTE has been long suspected, in line with the “two-hit” hypothesis of other forms of epilepsy,^{36,37} and genetic polymorphisms that putatively confer increased susceptibility have been identified.^{28,38} A family history of epilepsy was found to increase risk of PTE in children,^{39,40} but not in older patients.^{14,41}

Natural History

The natural history of PTE can involve a long latency, often several decades, between the inciting trauma and the first

late seizure. Although more than 80% of PTE begins within 2 years of TBI, the relative risk of developing PTE remains significantly elevated after >10 years in adults⁴¹ and in children.⁴⁰ Thus, vigilant long-term neurologic follow-up is essential. The so-called silent period before the onset of PTE also presents a unique opportunity for prophylaxis against epileptogenesis, and numerous interventions have been explored,^{28,42} including antiepileptic drugs (AEDs), inhibitors of intracellular signal transduction, ketogenic diet, therapeutic hypothermia, and exercise, although all remain investigational at present. In addition to monitoring for the onset of PTE, clinicians should be aware that an emerging concept of posttraumatic morbidogenesis frames epilepsy as one of several interconnected endophenotypes,^{43,44} which may each require special attention. Prolonged periods of seizure-freedom occur in up to half of patients with PTE,^{45,46} somewhat lower than remission rates in the epilepsy population as a whole.⁴⁷

Most early seizures after TBI are of the generalized tonic-clonic type,⁴⁸ whereas late seizures are more likely to have focal onset.⁴⁹ This pattern may be partially explained by the fact that generalized tonic-clonic seizures are easily recognized, whereas focal dyscognitive seizures (previously called *complex partial seizures*) may initially evade detection. Overall, about two-thirds of patients with PTE have seizures that are focal with secondary generalization,^{26,35} but other seizure types, including mesial temporal seizures related to hippocampal sclerosis,⁵⁰ *epilepsia partialis continua*,⁵¹ and interestingly, primary generalized seizures,⁴⁹ can result from trauma as well. The frontal and temporal lobes are most commonly affected in TBI, and this is reflected in the distribution of posttraumatic focal epilepsies (temporal > frontal >> occipital/parietal).⁴⁴

Diagnosis

As in any area of neurology, the diagnosis of PTE begins with the collection of a thorough history. Patients often will not volunteer certain incidences of head trauma (e.g., sports-related concussions or physical abuse with blows to the head),⁵² and these may only be elicited with focused questioning. Ascertainment bias is inevitable, but should not deter exploration of the circumstances of prior head trauma because the risk of PTE scales with the nature and severity of TBI.² Witnesses may be able to provide valuable collateral history, such as the duration of loss of consciousness and occurrence of immediate convulsions. Drug intoxication and withdrawal can be associated with both head injury and seizures,⁵³ and clinicians should be aware of these confounders. Once the history of head trauma is established, the possibility of seizures can be evaluated. Symptoms to screen for include premonitory aura, episodes of altered awareness or unresponsiveness, *déjà vu* or *jamais vu*, involuntary focal motor activity (e.g., clonic movements, hand and oroalimentary automatisms), dysphasia, olfactory or gustatory hallucinations, amnesia or periods of lost time, and unexplained nocturnal injuries or incontinence. In general, the presence of spells that are paroxysmal and

stereotyped should raise high suspicion for seizures.⁵⁴ Slow fluctuations in consciousness are often a prominent component of posttraumatic encephalopathy, but are not necessarily epileptic. Similarly, fleeting attentional lapses and cognitive changes that persist over long periods are unlikely to represent seizures. Psychogenic nonepileptic spells (PNES) are common after TBI,^{55,56} and are frequently mistaken for epileptic seizures.⁵⁷ Gold-standard diagnosis of PNES requires continuous video-electroencephalography (cVEEG) monitoring.⁵⁸

A neurologic exam may reveal deficits referable to cerebral injury, complementing neuroimaging, and in some cases, obviating the need for it.⁵⁹ In an acute setting, the exam should include evaluation for signs of skull fracture, level of consciousness, and focal motor or verbal deficits. Exam findings may help prognosticate long-term outcome after TBI,⁶⁰ and a variety of clinical scoring systems have been developed in this regard.^{61–63}

The EEG findings in TBI are usually nonspecific, and epileptiform activity on EEG does not predict disability outcome⁶⁴ or the development of PTE.⁶⁵ Notwithstanding recent efforts to develop objective EEG-based criteria for classifying TBI severity,^{66–68} EEG traditionally has been regarded as adding little clinical value in patients with TBI.⁶⁵ However, there is growing awareness that subclinical seizures, including nonconvulsive status epilepticus (NCSE), are relatively common after TBI^{69,70} and can only be detected by cVEEG.⁷¹ In one study of 87 pediatric patients who required intensive care unit (ICU) admission after TBI and were monitored by cVEEG, 42.5% had seizures and over one-third of these patients had subclinical seizures, mostly NCSE.⁷⁰ Nonconvulsive seizures have been associated with hippocampal atrophy,⁶⁹ so aggressive treatment is warranted. ICU management is often required for patients with moderate–severe TBI, and cVEEG should be considered for at least a subset of these patients to enable early detection and treatment of NCSE. In addition, some information from continuous EEG recordings, such as persistent impairment of α variability, may portend a worse prognosis after TBI.⁷²

Cranial imaging by computed tomography (CT) should be obtained urgently after moderate–severe TBI, and repeat CT is indicated for patients who develop seizures after initial imaging. In mild TBI, head CT prompted by posttraumatic seizures is often negative, but when positive, most commonly reveals intracranial hemorrhage,⁴⁸ which may be devastating without urgent surgical intervention. Beyond the acute setting, the mainstay of neuroimaging for PTE is magnetic resonance imaging (MRI), which provides the most sensitive means of defining the extent and severity of brain injury. Conventional MRI sequences, including T1-weighted, T2-weighted, gradient-echo, and diffusion-weighted imaging, may identify parenchymal hemorrhages, extra-axial blood products, early ischemia, edema, and gliosis. Advanced MRI techniques, such as susceptibility-weighted imaging and diffusion tensor imaging, are more sensitive to microhemorrhages and white matter injury, respectively,⁷³ and are being investigated for their potential to improve detection, to identify optimal treatments, and to predict outcomes.^{74–76}

Other forms of neuroimaging—magnetoencephalography,⁷⁷ single photon emission CT,⁷⁸ positron emission tomography,^{79,80} and EEG coupled with functional MRI⁸¹—are less prevalent in routine clinical practice, but may one day form the basis for a multimodal imaging-based approach to evaluating patients after TBI.

Management

The neurologic community has come a long way since the days when trephination was the mainstay of treating PTE.⁸² There is growing awareness of the clinical heterogeneity of PTE,⁴⁹ and optimal treatment can involve pharmacological and surgical options. Medical treatment is usually pursued first, and clinicians must therefore decide when to treat and with which drug. Unnecessary treatment with AEDs may impair neurorehabilitation after TBI,⁸³ and patients with post-TBI PNES should be treated with antidepressants, such as selective serotonin reuptake inhibitors (SSRIs), and/or cognitive–behavioral therapy (CBT)⁸⁴ rather than AEDs. After the diagnosis of PTE is confirmed, the necessity of pharmacotherapy depends on the temporal relationship between onset of seizures and the inciting TBI.

Convulsions are reasonably common in the immediate aftermath of concussive head trauma, and the pathogenesis may relate to brainstem dysfunction secondary to biomechanical forces inducing transient functional decerebration.⁸⁵ In a cohort of 22 Australian rugby players, concussive convulsions did not result in development of PTE over a mean follow-up of 3.5 years.⁸⁶ The prognosis is therefore thought to be universally excellent, and there is widespread agreement that AED therapy is not indicated.⁸⁷

By contrast, seizure prophylaxis with AEDs is part of standard therapy in the acute phase of moderate–severe TBI. Phenytoin (PHT) treatment significantly reduces the incidence of early posttraumatic seizures (14.2% to 3.6%),¹² and guidelines from the Brain Trauma Foundation and the American Academy of Neurology recommend AED treatment for the first 7 days after severe TBI.^{88,89} PHT has the most evidence for use in this setting, but more recently, levetiracetam (LEV) has gained popularity for post-TBI seizure prophylaxis.^{90,91} LEV has demonstrated comparable efficacy to PHT⁹² and is associated with fewer adverse effects and monitoring considerations.⁹³ At present, however, there are no prospective, double-blind, randomized controlled trials comparing LEV and PHT after TBI. As discussed above, the prognostic value of early posttraumatic seizures is controversial and early treatment with AEDs does not decrease the risk of PTE.^{12,94} Thus, AEDs are effective antiseizure drugs, but are not clearly antiepileptogenic, so AEDs are usually weaned one week after TBI.

Chronic AED treatment is indicated after a first late seizure due to the high risk of recurrence.³⁵ Principles of AED selection in PTE mirror those for other patients with epilepsy, and standard AEDs should all be effective.^{30,95} In many cases, given the paucity of evidence for superior efficacy of one AED over another,⁹⁶ AEDs are primarily selected based on consideration of the patient's comorbidities and the drug's spectrum of activity, anticipated side effects, titration rate, dosing

schedule, cost, and potential for drug-drug interactions.⁹⁷ There is no doctrine on duration of AED therapy, and much depends on a patient's age, personal preference, and drug tolerability. However, as a rule of thumb, AED withdrawal can be considered after at least 2 years of seizure-freedom, though waiting up to 4 years has been suggested as well.⁹⁸

Despite the development of over 15 third-generation AEDs since the 1980s,⁹⁹ 30 to 40% of patients with epilepsy have seizures that are incompletely controlled with medications alone.¹⁰⁰ Medical intractability is predicted after failure of two antiepileptic drugs,¹⁰¹ and poor prognostic factors include the presence of structural cerebral abnormalities,⁴⁷ such as can be seen in PTE. In some medically refractory patients, surgical resection of the epileptogenic tissue is highly effective,¹⁰² and recent evidence supports early consideration of surgical treatment.¹⁰³ A patient's candidacy for resective surgery hinges on precise seizure localization by cVEEG and neuroimaging, and the likelihood of seizure-freedom depends on temporal versus extratemporal ictal onset and on the presence or absence of an identifiable lesion.¹⁰⁴ Although epilepsy surgery remains underutilized overall,¹⁰⁵ the frequent presence of focal cerebral pathology in patients with PTE often prompts consideration of surgical options. For example, mesial temporal sclerosis (MTS) is a common pathology in PTE despite the presence of multifocal injury.^{50,106} Rates of seizure freedom in selected patients with mesial temporal lobe epilepsy (MTLE) who undergo temporal lobectomy can be as high as 80 to 90%,^{107,108} and patients with posttraumatic MTLE may therefore be particularly good candidates for epilepsy surgery.¹⁰⁹ Indeed, surgical outcomes for MTLE are comparable between traumatic and nontraumatic patient populations.¹⁰⁶ Patients with PTE of neocortical origin are less ideal surgical candidates,^{50,109} but those with focal encephalomalacia can have good outcomes with electrocorticography-guided resections.¹¹⁰

Enthusiasm for surgical resection in patients with medically refractory PTE should be tempered by several considerations: (1) As a group, patients with PTE have seizure foci that are difficult to localize accurately,¹⁰⁹ partly due to technical issues related to prior craniotomies and breach rhythms¹¹¹ and because of frequent involvement of the frontal lobes; (2) TBI frequently produces diffuse cerebral injury, which can result in multifocal epilepsy and/or seizure-onset zones that overlap with eloquent brain regions; and (3) scar tissue and adhesions related to the inciting trauma can increase the risk for surgical complications.¹¹⁰

For patients with medically refractory PTE who are poor candidates for definitive resection, vagus nerve stimulation (VNS)¹¹² should be considered for adjunctive treatment. Vagus nerve stimulation involves a device implanted in the neck for open-loop peripheral stimulation of the vagus nerve, which is thought to provide indirect seizure control via retrograde brain inhibition.¹¹³ Although prospective clinical trial data in patients with PTE are lacking, one case-control study found that VNS was associated with greater reduction in seizure frequency in patients with PTE than in patients with non-PTE at 2 years of follow-up (78% vs. 61% of patients with > 50% reduction in seizure frequency).¹¹⁴

More recently, a direct form of neuromodulation, called *responsive neurostimulation* (RNS), has emerged as a promising therapy for patients with medically refractory epilepsy.^{115,116} Unlike VNS, the RNS system functions in a closed-loop manner, detecting incipient seizure activity with implanted intracranial electrodes and then counterstimulating to terminate seizures via a small, programmable neurostimulator seated in a skull cassette. Optimal candidates for RNS are adults with multifocal seizure onsets and/or seizure foci that are not amenable to surgical resection due to overlap with eloquent brain regions. Over 2 years of follow-up, more than half of patients with RNS experienced at least a 50% reduction in seizure frequency.¹¹⁷ A related technology, deep brain (anterior thalamic nucleus) stimulation,¹¹⁸ has been approved in several countries and may soon be available in the United States.¹¹⁹ Although not without controversy,¹²⁰ neurostimulation for epilepsy continues to evolve rapidly, expanding the clinician's armamentarium for treating medically refractory PTE. A strategy for navigating the various diagnostic and treatment options in PTE is outlined in ►Fig. 1, which expands upon a previously proposed algorithm.⁹⁵

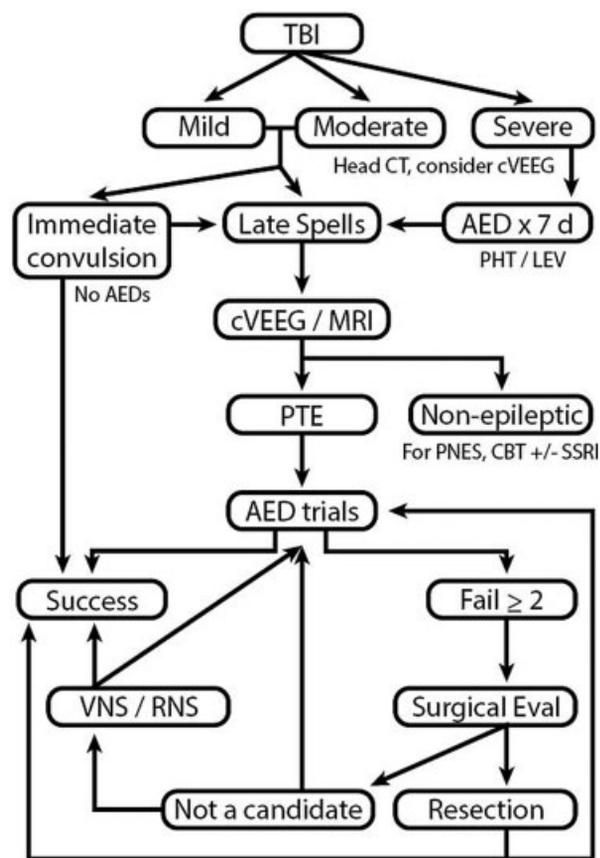


Fig. 1 An algorithm for the management of posttraumatic epilepsy. AED, antiepileptic drug; CBT, cognitive-behavioral therapy; CT, computed tomography; cVEEG, continuous video-electroencephalography; LEV, levetiracetam; MRI, magnetic resonance imaging; PHT, phenytoin; PNES, psychogenic nonepileptic spell; PTE, posttraumatic epilepsy; RNS, responsive neurostimulation; SSRI, selective serotonin reuptake inhibitors; TBI, traumatic brain injury; VNS, vagus nerve stimulation.

Conclusion

Traumatic brain injury is a rapidly growing epidemic and PTE often follows in its wake. Traumatic brain injury offers a unique opportunity for prophylaxis against epileptogenesis, but once developed, PTE is a heterogeneous condition that can be challenging to treat. Clinicians should be aware of the natural history of PTE and the shifting landscape concerning diagnostic and treatment options.

References

- Penfield W. Introduction (Symposium on post-traumatic epilepsy). *Epilepsia* 1961;2:109–110
- Lowenstein DH. Epilepsy after head injury: an overview. *Epilepsia* 2009;50(Suppl 2):4–9
- Temkin O. *The Falling Sickness: A History of Epilepsy from the Greeks to the Beginnings of Modern Neurology*. Baltimore, MD: The Johns Hopkins University Press; 1945
- Faul M, Xu L, Wald MM, et al. *Traumatic Brain Injury in the United States: Emergency Department Visits, Hospitalizations and Deaths 2002–2006*. Atlanta, GA: Centers for Disease Control and Prevention and National Center for Injury Prevention and Control; 2010
- Maas AI, Stocchetti N, Bullock R. Moderate and severe traumatic brain injury in adults. *Lancet Neurol* 2008;7(8):728–741
- Hyder AA, Wunderlich CA, Puvanachandra P, Gururaj G, Kobusingye OC. The impact of traumatic brain injuries: a global perspective. *NeuroRehabilitation* 2007;22(5):341–353
- Rusnak M. Traumatic brain injury: giving voice to a silent epidemic. *Nat Rev Neurol* 2013;9(4):186–187
- Langlois JA, Marr A, Mitchko J, Johnson RL. Tracking the silent epidemic and educating the public: CDC's traumatic brain injury-associated activities under the TBI Act of 1996 and the Children's Health Act of 2000. *J Head Trauma Rehabil* 2005;20(3):196–204
- Chang BS, Lowenstein DH. Epilepsy. *N Engl J Med* 2003;349(13):1257–1266
- England MJ, Liverman CT, Schultz AM, Strawbridge LM. Epilepsy across the spectrum: promoting health and understanding. A summary of the Institute of Medicine report. *Epilepsy Behav* 2012;25(2):266–276
- Agrawal A, Timothy J, Pandit L, Manju M. Post-traumatic epilepsy: an overview. *Clin Neurol Neurosurg* 2006;108(5):433–439
- Temkin NR, Dikmen SS, Wilensky AJ, Keihm J, Chabal S, Winn HR. A randomized, double-blind study of phenytoin for the prevention of post-traumatic seizures. *N Engl J Med* 1990;323(8):497–502
- Hauser WA, Annegers JF, Kurland LT. Incidence of epilepsy and unprovoked seizures in Rochester, Minnesota: 1935–1984. *Epilepsia* 1993;34(3):453–468
- Salazar AM, Jabbari B, Vance SC, Grafman J, Amin D, Dillon JD. Epilepsy after penetrating head injury. I. Clinical correlates: a report of the Vietnam Head Injury Study. *Neurology* 1985;35(10):1406–1414
- Herman ST. Epilepsy after brain insult: targeting epileptogenesis. *Neurology* 2002;59(9, Suppl 5):S21–S26
- Zarocostas J. Proliferation of firearms is growing global health problem. *BMJ* 2007;335(7618):470–471
- Snell FI, Halter MJ. A signature wound of war. *J Psychosoc Nurs Ment Health Serv* 2010;•••:1–7
- Kovacs SK, Leonessa F, Ling GS. Blast TBI models, neuropathology, and implications for seizure risk. *Front Neurol* 2014;5:47
- Pugh MJ, Orman JA, Jaramillo CA, et al. The prevalence of epilepsy and association with traumatic brain injury in veterans of the Afghanistan and Iraq wars. *J Head Trauma Rehabil* 2014
- Wilde EA, Whiteneck GG, Bogner J, et al. Recommendations for the use of common outcome measures in traumatic brain injury research. *Arch Phys Med Rehabil* 2010;91(11):1650–1660.e17
- Bushnik T, Englander J, Duong T. Medical and social issues related to posttraumatic seizures in persons with traumatic brain injury. *J Head Trauma Rehabil* 2004;19(4):296–304
- Ferguson PL, Smith GM, Wannamaker BB, Thurman DJ, Picklesimer EE, Selassie AW. A population-based study of risk of epilepsy after hospitalization for traumatic brain injury. *Epilepsia* 2010;51(5):891–898
- Annegers JF, Coan SP. The risks of epilepsy after traumatic brain injury. *Seizure* 2000;9(7):453–457
- Annegers JF, Hauser WA, Coan SP, Rocca WA. A population-based study of seizures after traumatic brain injuries. *N Engl J Med* 1998;338(1):20–24
- Annegers JF, Grabow JD, Groover RV, Laws ER Jr, Elveback LR, Kurland LT. Seizures after head trauma: a population study. *Neurology* 1980;30(7 Pt 1):683–689
- Englander J, Bushnik T, Duong TT, et al. Analyzing risk factors for late posttraumatic seizures: a prospective, multicenter investigation. *Arch Phys Med Rehabil* 2003;84(3):365–373
- Skandsen T, Ivar Lund T, Fredriksli O, Vik A. Global outcome, productivity and epilepsy 3–8 years after severe head injury. The impact of injury severity. *Clin Rehabil* 2008;22(7):653–662
- Pitkänen A, Immonen R. Epilepsy related to traumatic brain injury. *Neurotherapeutics* 2014;11(2):286–296
- Wang H, Xin T, Sun X, et al. Post-traumatic seizures—a prospective, multicenter, large case study after head injury in China. *Epilepsy Res* 2013;107(3):272–278
- Langendorf FG, Pedley TA, Temkin NR. Posttraumatic Seizures. In: Engel J Jr., Pedley TA, eds. *Epilepsy: A Comprehensive Textbook*. 2nd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2008:2537–2542
- Berg AT, Shinnar S. The risk of seizure recurrence following a first unprovoked seizure: a quantitative review. *Neurology* 1991;41(7):965–972
- 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(5):584–589
- Temkin NR. Risk factors for posttraumatic seizures in adults. *Epilepsia* 2003;44(Suppl 10):18–20
- Kollebold T. Immediate and early cerebral seizures after head injuries. Part III. *J Oslo City Hosp* 1978;28(6):77–86
- Haltiner AM, Temkin NR, Dikmen SS. Risk of seizure recurrence after the first late posttraumatic seizure. *Arch Phys Med Rehabil* 1997;78(8):835–840
- Hamelin S, Pouyatou B, Khalaf-Nazzal R, et al. Long-term modifications of epileptogenesis and hippocampal rhythms after prolonged hyperthermic seizures in the mouse. *Neurobiol Dis* 2014;69:156–168
- Scheffer IE. Epilepsy genetics revolutionizes clinical practice. *Neuropediatrics* 2014;45(2):70–74
- Davidson J, Cusimano MD, Bendena WG. Post-traumatic brain injury: genetic susceptibility to outcome. *Neuroscientist* 2014; ePub ahead of print PubMed
- Christensen J, Pedersen MG, Pedersen CB, Sidenius P, Olsen J, Vestergaard M. Long-term risk of epilepsy after traumatic brain injury in children and young adults: a population-based cohort study. *Lancet* 2009;373(9669):1105–1110
- Hung R, Carroll LJ, Cancelliere C, et al. Systematic review of the clinical course, natural history, and prognosis for pediatric mild traumatic brain injury: results of the International Collaboration on Mild Traumatic Brain Injury Prognosis. *Arch Phys Med Rehabil* 2014;95(3, Suppl): S174–S191
- Raymont V, Salazar AM, Krueger F, Grafman J. “Studying injured minds” - the Vietnam head injury study and 40 years of brain injury research. *Front Neurol* 2011;2:15

- 42 Smith BN. Prophylaxis for post-traumatic epilepsy: can your kinase do that? *Epilepsy Curr* 2014;14(1):38–40
- 43 Pitkänen A, Kempainen S, Ndoe-Ekane XE, et al. Posttraumatic epilepsy - disease or comorbidity? *Epilepsy Behav* 2014
- 44 Diaz-Arrastia R, Agostini MA, Madden CJ, Van Ness PC. Posttraumatic epilepsy: the endophenotypes of a human model of epileptogenesis. *Epilepsia* 2009;50(Suppl 2):14–20
- 45 Frey LC. Epidemiology of posttraumatic epilepsy: a critical review. *Epilepsia* 2003;44(Suppl 10):11–17
- 46 Caveness WF. Onset and cessation of fits following craniocerebral trauma. *J Neurosurg* 1963;20:570–583
- 47 Kwan P, Sander JW. The natural history of epilepsy: an epidemiological view. *J Neurol Neurosurg Psychiatry* 2004;75(10):1376–1381
- 48 Lee ST, Lui TN. Early seizures after mild closed head injury. *J Neurosurg* 1992;76(3):435–439
- 49 Gupta PK, Sayed N, Ding K, et al. Subtypes of post-traumatic epilepsy: clinical, electrophysiological, and imaging features. *J Neurotrauma* 2014;31(16):1439–1443
- 50 Diaz-Arrastia R, Agostini MA, Frol AB, et al. Neurophysiologic and neuroradiologic features of intractable epilepsy after traumatic brain injury in adults. *Arch Neurol* 2000;57(11):1611–1616
- 51 Shrivastava V, Burji NP, Basumatary LJ, Das M, Goswami M, Kayal AK. Etiological profile of epilepsia partialis continua among adults in a tertiary care hospital. *Neurol India* 2013;61(2):156–160
- 52 Hung C, Chen JW. Treatment of post-traumatic epilepsy. *Curr Treat Options Neurol* 2012;14(4):293–306
- 53 Medvdovsky M, Ifergane G, Wirguin I, et al. Traumatic intracranial hemorrhage in patients with seizures: descriptive characteristics. *Epilepsy Behav* 2006;8(2):429–433
- 54 Cornes SB, Shih T. Evaluation of the patient with spells. *Continuum (Minneapolis)* 2011;17(5 Neurologic Consultation in the Hospital):984–1009
- 55 Salinsky M, Storzbach D, Goy E, Evrard C. Traumatic brain injury and psychogenic seizures in veterans. *J Head Trauma Rehabil* 2014
- 56 Chen LL, Baca CB, Choe J, Chen JW, Ayad ME, Cheng EM. Posttraumatic epilepsy in Operation Enduring Freedom/Operation Iraqi Freedom veterans. *Mil Med* 2014;179(5):492–496
- 57 Barry E, Krumholz A, Bergrey GK, Chatha H, Alemayehu S, Grattan L. Nonepileptic posttraumatic seizures. *Epilepsia* 1998;39(4):427–431
- 58 Sahaya K, Dholakia SA, Sahota PK. Psychogenic non-epileptic seizures: a challenging entity. *J Clin Neurosci* 2011;18(12):1602–1607
- 59 Aziz H, Rhee P, Pandit V, et al. Mild and moderate pediatric traumatic brain injury: replace routine repeat head computed tomography with neurologic examination. *J Trauma Acute Care Surg* 2013;75(4):550–554
- 60 Walker WC, McDonald SD. Does neurologic examination during inpatient rehabilitation help predict global outcome after non-penetrating traumatic brain injury? *PM R* 2011;3(1):6–12
- 61 Luoto TM, Silverberg ND, Kataja A, et al. Sport concussion assessment tool 2 in a civilian trauma sample with mild traumatic brain injury. *J Neurotrauma* 2014;31(8):728–738
- 62 Okasha AS, Fayed AM, Saleh AS. The FOUR score predicts mortality, endotracheal intubation and ICU length of stay after traumatic brain injury. *Neurocrit Care* 2014;21(3):496–504
- 63 McNett M, Amato S, Gianakis A, et al. The FOUR score and GCS as predictors of outcome after traumatic brain injury. *Neurocrit Care* 2014;21(1):52–57
- 64 Steinbaugh LA, Lindsell CJ, Shutter LA, Szaflarski JP. Initial EEG predicts outcomes in a trial of levetiracetam vs. fosphenytoin for seizure prevention. *Epilepsy Behav* 2012;23(3):280–284
- 65 Jennett B, Van De Sande J. EEG prediction of post-traumatic epilepsy. *Epilepsia* 1975;16(2):251–256
- 66 Prichep LS, Ghosh Dastidar S, Jacquin A, et al. Classification algorithms for the identification of structural injury in TBI using brain electrical activity. *Comput Biol Med* 2014;53:125–133
- 67 Thatcher RW, North DM, Curtin RT, et al. An EEG severity index of traumatic brain injury. *J Neuropsychiatry Clin Neurosci* 2001;13(1):77–87
- 68 Tebano MT, Cameroni M, Gallozzi G, et al. EEG spectral analysis after minor head injury in man. *Electroencephalogr Clin Neurophysiol* 1988;70(2):185–189
- 69 Vespa PM, McArthur DL, Xu Y, et al. Nonconvulsive seizures after traumatic brain injury are associated with hippocampal atrophy. *Neurology* 2010;75(9):792–798
- 70 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(10):1780–1788
- 71 Maganti RK, Rutecki P. EEG and epilepsy monitoring. *Continuum (Minneapolis)* 2013;19(3 Epilepsy):598–622
- 72 Vespa PM, Boscardin WJ, Hovda DA, et al. Early and persistent impaired percent alpha variability on continuous electroencephalography monitoring as predictive of poor outcome after traumatic brain injury. *J Neurosurg* 2002;97(1):84–92
- 73 Kou Z, Wu Z, Tong KA, et al. The role of advanced MR imaging findings as biomarkers of traumatic brain injury. *J Head Trauma Rehabil* 2010;25(4):267–282
- 74 Hunter JV, Wilde EA, Tong KA, Holshouser BA. Emerging imaging tools for use with traumatic brain injury research. *J Neurotrauma* 2012;29(4):654–671
- 75 Fox WC, Park MS, Belverud S, Klugh A, Rivet D, Tomlin JM. Contemporary imaging of mild TBI: the journey toward diffusion tensor imaging to assess neuronal damage. *Neurol Res* 2013;35(3):223–232
- 76 Immonen R, Kharatishvili I, Gröhn O, Pitkänen A. MRI biomarkers for post-traumatic epileptogenesis. *J Neurotrauma* 2013;30(14):1305–1309
- 77 Lewine JD, Davis JT, Bigler ED, et al. Objective documentation of traumatic brain injury subsequent to mild head trauma: multimodal brain imaging with MEG, SPECT, and MRI. *J Head Trauma Rehabil* 2007;22(3):141–155
- 78 Raji CA, Tarzwell R, Pavel D, et al. Clinical utility of SPECT neuroimaging in the diagnosis and treatment of traumatic brain injury: a systematic review. *PLoS ONE* 2014;9(3):e91088
- 79 Selwyn R, Hockenbury N, Jaiswal S, Mathur S, Armstrong RC, Byrnes KR. Mild traumatic brain injury results in depressed cerebral glucose uptake: an (18)FDG PET study. *J Neurotrauma* 2013;30(23):1943–1953
- 80 Hong YT, Veenith T, Dewar D, et al. Amyloid imaging with carbon 11-labeled Pittsburgh compound B for traumatic brain injury. *JAMA Neurol* 2014;71(1):23–31
- 81 Storti SF, Formaggio E, Franchini E, et al. A multimodal imaging approach to the evaluation of post-traumatic epilepsy. *MAGMA* 2012;25(5):345–360
- 82 Jensen RL, Stone JL. Benjamin Winslow Dudley and early American trephination for posttraumatic epilepsy. *Neurosurgery* 1997;41(1):263–268
- 83 Hernandez TD, Naritoku DK. Seizures, epilepsy, and functional recovery after traumatic brain injury: a reappraisal. *Neurology* 1997;48(4):803–806
- 84 LaFrance WC Jr, Baird GL, Barry JJ, et al; NES Treatment Trial (NEST-T) Consortium. Multicenter pilot treatment trial for psychogenic nonepileptic seizures: a randomized clinical trial. *JAMA Psychiatry* 2014;71(9):997–1005
- 85 McCrory PR, Berkovic SF. Video analysis of acute motor and convulsive manifestations in sport-related concussion. *Neurology* 2000;54(7):1488–1491
- 86 McCrory PR, Bladin PF, Berkovic SF. Retrospective study of concussive convulsions in elite Australian rules and rugby league

- footballers: phenomenology, aetiology, and outcome. *BMJ* 1997; 314(7075):171–174
- 87 Perron AD, Brady WJ, Huff JS. Concussive convulsions: emergency department assessment and management of a frequently misunderstood entity. *Acad Emerg Med* 2001;8(3):296–298
- 88 Bratton SL, Chestnut RM, Ghajar J, et al; Brain Trauma Foundation; American Association of Neurological Surgeons; Congress of Neurological Surgeons; Joint Section on Neurotrauma and Critical Care, AANS/CNS. Guidelines for the management of severe traumatic brain injury. XIII. Antiseizure prophylaxis. *J Neurotrauma* 2007;24(Suppl 1):S83–S86
- 89 Chang BS, Lowenstein DH; Quality Standards Subcommittee of the American Academy of Neurology. Practice parameter: anti-epileptic drug prophylaxis in severe traumatic brain injury: report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology* 2003;60(1):10–16
- 90 Szaflarski JP, Nazzari Y, Dreier LE. Post-traumatic epilepsy: current and emerging treatment options. *Neuropsychiatr Dis Treat* 2014; 10:1469–1477
- 91 Krueger 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(5):883.e9–883.e13
- 92 Szaflarski JP, Sangha KS, Lindsell CJ, Shutter LA. Prospective, randomized, single-blinded comparative trial of intravenous levetiracetam versus phenytoin for seizure prophylaxis. *Neurocrit Care* 2010;12(2):165–172
- 93 Torbic H, Forni AA, Anger KE, Degradó JR, Greenwood BC. Use of antiepileptics for seizure prophylaxis after traumatic brain injury. *Am J Health Syst Pharm* 2013;70(9):759–766
- 94 Temkin NR. Preventing and treating posttraumatic seizures: the human experience. *Epilepsia* 2009;50(Suppl 2):10–13
- 95 Burneo JG, Sirven JI, Kiesel LW, et al. Managing common complex symptomatic epilepsies: tumors and trauma: American Epilepsy Society - 2012 annual course summary. *Epilepsy Curr* 2013; 13(5):232–235
- 96 Glauser T, Ben-Menachem E, Bourgeois B, et al; ILAE Subcommittee on AED Guidelines. Updated ILAE evidence review of anti-epileptic drug efficacy and effectiveness as initial monotherapy for epileptic seizures and syndromes. *Epilepsia* 2013;54(3): 551–563
- 97 Fountain NB. Choosing among antiepileptic drugs. *Continuum (Minneapolis)* 2010;16(3 Epilepsy):121–135
- 98 Camfield P, Camfield C. When is it safe to discontinue AED treatment? *Epilepsia* 2008;49(Suppl 9):25–28
- 99 Löscher W, Klitgaard H, Twyman RE, Schmidt D. New avenues for anti-epileptic drug discovery and development. *Nat Rev Drug Discov* 2013;12(10):757–776
- 100 Brodie MJ. Road to refractory epilepsy: the Glasgow story. *Epilepsia* 2013;54(Suppl 2):5–8
- 101 Kwan P, Brodie MJ. Early identification of refractory epilepsy. *N Engl J Med* 2000;342(5):314–319
- 102 Wiebe S, Blume WT, Girvin JP, Eliasziw M; Effectiveness and Efficiency of Surgery for Temporal Lobe Epilepsy Study Group. A randomized, controlled trial of surgery for temporal-lobe epilepsy. *N Engl J Med* 2001;345(5):311–318
- 103 Engel J Jr, McDermott MP, Wiebe S, et al; Early Randomized Surgical Epilepsy Trial (ERSET) Study Group. Early surgical therapy for drug-resistant temporal lobe epilepsy: a randomized trial. *JAMA* 2012;307(9):922–930
- 104 Benbadis SR, Tatum WO, Vale FL. When drugs don't work: an algorithmic approach to medically intractable epilepsy. *Neurology* 2000;55(12):1780–1784
- 105 Englot DJ, Ouyang D, Garcia PA, Barbaro NM, Chang EF. Epilepsy surgery trends in the United States, 1990–2008. *Neurology* 2012; 78(16):1200–1206
- 106 Hartzfeld P, Elisevich K, Pace M, Smith B, Gutierrez JA. Characteristics and surgical outcomes for medial temporal post-traumatic epilepsy. *Br J Neurosurg* 2008;22(2):224–230
- 107 Elliott RE, Bollo RJ, Berliner JL, et al. Anterior temporal lobectomy with amygdalohippocampectomy for mesial temporal sclerosis: predictors of long-term seizure control. *J Neurosurg* 2013; 119(2):261–272
- 108 Spencer S, Huh L. Outcomes of epilepsy surgery in adults and children. *Lancet Neurol* 2008;7(6):525–537
- 109 Marks DA, Kim J, Spencer DD, Spencer SS. Seizure localization and pathology following head injury in patients with uncontrolled epilepsy. *Neurology* 1995;45(11):2051–2057
- 110 Hakimian S, Kershenovich A, Miller JW, et al. Long-term outcome of extratemporal resection in posttraumatic epilepsy. *Neurosurg Focus* 2012;32(3):E10
- 111 Brigo F, Cicero R, Fiaschi A, Bongiovanni LG. The breach rhythm. *Clin Neurophysiol* 2011;122(11):2116–2120
- 112 Morris GL III, Gloss D, Buchhalter J, Mack KJ, Nickels K, Harden C. Evidence-based guideline update: vagus nerve stimulation for the treatment of epilepsy: report of the Guideline Development Subcommittee of the American Academy of Neurology. *Neurology* 2013;81(16):1453–1459
- 113 Vale FL, Ahmadian A, Youssef AS, Tatum WO, Benbadis SR. Long-term outcome of vagus nerve stimulation therapy after failed epilepsy surgery. *Seizure* 2011;20(3):244–248
- 114 Englot DJ, Rolston JD, Wang DD, Hassnain KH, Gordon CM, Chang EF. Efficacy of vagus nerve stimulation in posttraumatic versus nontraumatic epilepsy. *J Neurosurg* 2012;117(5):970–977
- 115 Ben-Menachem E, Krauss GL. Epilepsy: responsive neurostimulation-modulating the epileptic brain. *Nat Rev Neurol* 2014; 10(5):247–248
- 116 Morrell MJ; RNS System in Epilepsy Study Group. Responsive cortical stimulation for the treatment of medically intractable partial epilepsy. *Neurology* 2011;77(13):1295–1304
- 117 Heck CN, King-Stephens D, Massey AD, et al. Two-year seizure reduction in adults with medically intractable partial onset epilepsy treated with responsive neurostimulation: final results of the RNS System Pivotal trial. *Epilepsia* 2014;55(3):432–441
- 118 Fisher R, Salanova V, Witt T, et al; SANTE Study Group. Electrical stimulation of the anterior nucleus of thalamus for treatment of refractory epilepsy. *Epilepsia* 2010;51(5):899–908
- 119 Fisher RS, Velasco AL. Electrical brain stimulation for epilepsy. *Nat Rev Neurol* 2014;10(5):261–270
- 120 So NK, Cole AJ, Tandon N, Slater JD, Smith MC. Neurostimulation for the treatment of epilepsy: the skeptical view. *Neurology* 2014; 83(9):847–849