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Doctors Galang, Ferimer, and Wagner have reported no relevant relationships with proprietary entities producing health care goods or services.

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Traumatic Brain Injury and Post-Traumatic Epilepsy: Current Practice and Future Proposals for an Individualized Approach

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Clinical Vignette

MB, a 40-year-old, left-hand dominant, male mechanic with no significant past medical history, sustained a traumatic brain injury (TBI) after an ATV accident. MB was an unhelmeted driver whose vehicle flipped over a steep ravine. He lost consciousness for approximately five minutes as reported by a fellow rider who was with him. MB was pinned under the ATV and sustained multiple crush injuries, as well as second degree burns to his legs. The EMT documented a Glasgow Coma Scale (GCS) of 7 (eye response-2, verbal response-1, motor response-4) at the scene of the collision. Pupils were equal and reactive. MB required intubation to maintain an airway. He was transported by helicopter to our level I trauma facility 100 miles from the scene of injury. At the hospital, CT head without contrast was obtained, which showed extensive facial fractures and left subdural or subarachnoid hemorrhage (see Figure 1).



FIGURE 1: CT scan image with an example of a left subdural or subarachnoid hemorrhage after receiving IV contrast.

MB's injuries required emergent left-sided hemicraniectomy. While in the ICU, he was started on phenytoin with an initial dose of 15 mg/kg IV followed by daily dosing at a rate no greater than 25 mg/min. On day three in the ICU, he became tachypneic, tachycardic (with a heart rate in the 120s), and diaphoretic. The clinical staff documented muscle rigidity of his upper and lower extremities, and he was afebrile. MB had three specific episodes with these findings during the day. Each episode lasted approximately two minutes, and then vitals returned to baseline. EEG monitoring was performed for 24 hours, which showed focal arrhythmic (polymorphic) slow activity and sharp waves originating from the left temporal region around the time of the change in vital signs and muscle rigidity. Phenytoin was discontinued, and the patient was started on phenobarbital IV. A day later, his vitals improved. A continuous EEG monitor for 24 hours documented no further seizure activity. Phenobarbital was discontinued on day eight post-injury, and MB was started on valproate. Dosing was regulated by monitoring his serum valproate levels. He also had an extensive ICU stay of 14 days due to respiratory failure requiring tracheostomy and dysphagia requiring percutaneous endoscopic gastrostomy placement (PEG). It was documented that MB later developed a rash while on valproate that was discontinued. The physical medicine and rehabilitation consultation service was asked to evaluate for appropriate therapy for seizure treatment and rehabilitation management 15 days post-TBI.

TBI and Seizures

The Centers for Disease Control reported in 2010 that TBI resulted in approximately 2.5 million emergency department visits, hospitalizations, or deaths.¹ Common neurological sequelae following TBI may include: memory impairment, difficulty with focus or attention to tasks, problems with emotional control, challenges with coordination or balance, motor weakness in the extremities, and/or changes in perceptual sensory abilities.² TBI disrupts the tissue responsible for electrical firing, which may lead to epileptogenesis (seizures).³ Seizures can be classified by several terms. Post-traumatic seizure (PTS) is defined as “post-traumatic” because the seizure occurred in relation to, or was provoked by, the TBI.^{4,5} Seizures occurring after TBI are classified further according to when they occur. An early post-traumatic seizure (early PTS) is defined as a seizure during the first week after the brain injury, whereas a late post-traumatic seizure (late PTS) is defined as occurring more than seven days after the brain injury.³ According to recent definitions published by the International League Against Epilepsy (ILAE), post-traumatic epilepsy (PTE) is defined as one or more unprovoked seizures more than seven days out from injury⁶, essentially rendering individuals with late PTS as having PTE.

Epidemiology

PTE risk is related to severity of the TBI. In a population-based study of 4,541 subjects, the seizure incidence increased with severity of injury (mild injury=1.5 relative risk, moderate injury=2.9, and severe injury=17).⁷ The rates of early PTS and late PTS vary between studies. In a multicenter study with over 600 subjects more than 16 years old, the rate of early PTS was 3%.⁸ This same study also reported that the probability of late PTS varied depending on whether a patient experienced early PTS (rate of late PTS after early PTS=26.2% versus rate of late PTS if no incidence of early PTS=13.1%).⁸ Further analysis determined that type of traumatic injury and location of injury also can affect late PTS incidence. One report suggests that in the setting of a depressed skull fracture, there can be up to a 12.3% prevalence of early PTE.⁹ PTE has been reported in 20% of the population having symptomatic seizures, and 5% of all patients with seizure have PTE.⁸ Based on previous literature, individuals who are at risk for PTS tend to have the characteristics described in Figure 2 on Page 3.

Proposed Molecular Mechanisms That Contribute to PTE

Recent genetic studies have evaluated whether the adenosinergic, glutamatergic, and GABAergic neurotransmitter systems contribute to the variable risk for PTE. In general, PTE complicates about 3–5% of moderate cases of TBI and up to 25–50% of cases of severe TBI.¹¹ Despite some evidence supporting clinical risk factors for PTS, criteria are lacking to accurately predict who is at risk for PTS. Thus, researchers are beginning to analyze personal biology and the role genetics play in recovery and post-injury symptomatology. Through a translational laboratory-to-clinic approach, clinicians may be closer to analyzing an individual's genetic profile to identify, for example, those who are more susceptible to seizures and what anti-epileptic treatment may be appropriate based on clinical trials.¹² Figure 3 on Page 4 is a visual representation of the different factors that affect PTE risk after TBI.

Adenosine is a potent endogenous neurotransmitter and anticonvulsant, and adenosine levels are regulated by astrocytes. Astrocytes are supportive glial cells that facilitate interactions between neuronal cell bodies and other extracellular brain tissues (e.g., blood vessels, gray matter, and white matter). Astrocytes and microglia cells are both implicated in neuronal cell death. In response to brain injury, astrocytes can attempt to promote repair, but if this reaction is overactive, it can lead to reactive astrogliosis, otherwise known as glial scarring. Astrogliosis can result in the over-expression of adenosine kinase (ADK),

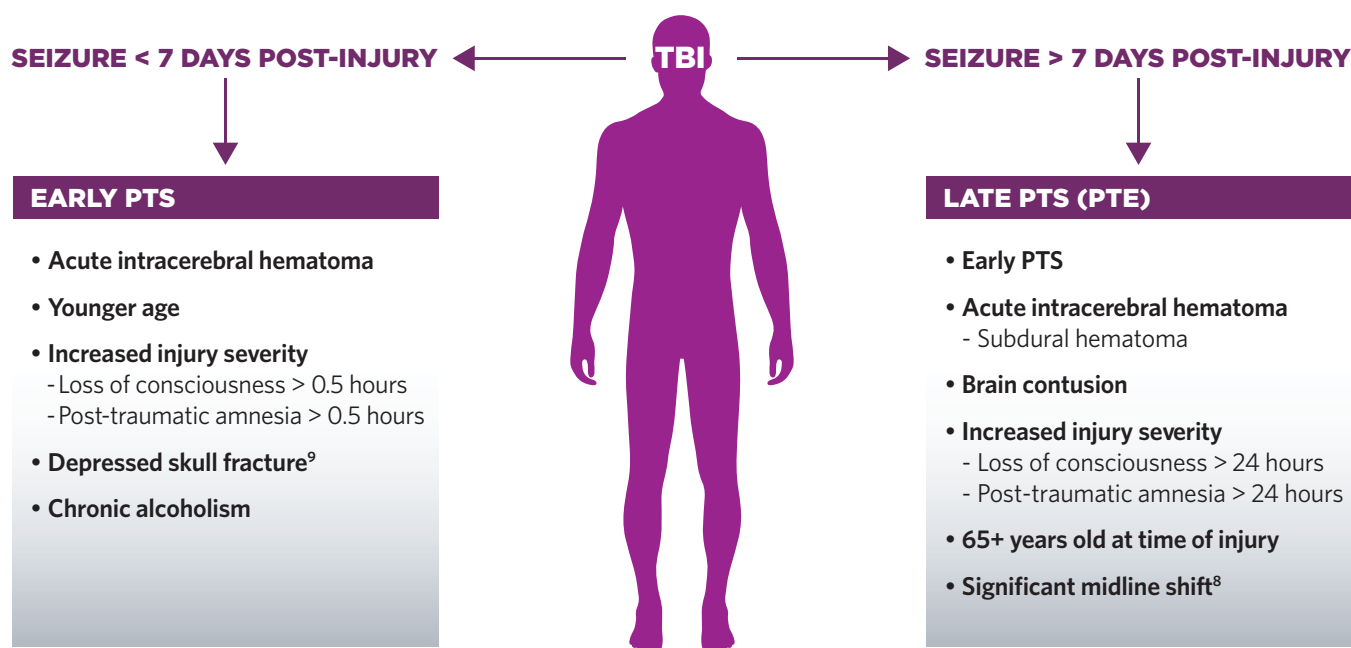


FIGURE 2: Risk Factors for Early and Late PTS¹⁰

which can then result in reduced adenosine levels,¹³ leaving those areas of the brain, such as the hippocampus, vulnerable to epileptogenic activity after TBI.¹³ In fact, experimental models show that scar formation is a major cause for epileptogenesis and the eventual development of seizures, at least in part by altered adenosine kinase (ADK) expression.¹³ Also, work has shown that genes governing the adenosine regulatory cycle¹⁴ and adenosine A1 target receptors¹⁵ can increase the probability of PTE and accelerate the process of epileptogenesis that often occurs after severe TBI.¹⁴

Another inhibitory neurotransmitter system implicated in the pathology of PTE is gamma-aminobutyric acid (GABA). Among other actions, GABA neurotransmitter systems regulate excitatory tone.¹⁶ GABA is synthesized via the enzymatic actions of glutamic acid decarboxylase (GAD) on glutamate, and its actions are connected to experimental seizure models.¹⁷ Genetic variation within the GAD1 gene has been linked in one study to PTE risk¹⁸, particularly when occurring over the first six months post-injury. In addition, inflammation is a known mechanism facilitating epileptogenesis and the eventual development of seizures.

Together, these data show the potential importance of personal biology in gauging PTE risk. Further studies on this topic are needed to help develop personalized algorithms aimed at optimal screening, prophylaxis, and treatments after TBI. Similarly, experimental models of TBI and epilepsy can help to understand

PTE and determine how to best treat it. Animal models of TBI can be used to determine more about how anticonvulsant medications affect the injured brain. For example, the controlled cortical impact injury (CCI) model has been used to demonstrate the adverse CNS effects of chronic phenytoin use on the injured brain.¹⁹ In contrast, this same model has also demonstrated that daily use of levetiracetam has multiple neuroprotective properties, normalizing brain tissue levels of markers of inflammation (IL-1b) and excitotoxicity (glutamate transporters).²⁰

Recognizing Seizures After TBI

Individuals with TBI may exhibit signs and symptoms of seizures, which may present with a variety of atypical symptoms like fluttering of eyes, confusion, difficulty with speech, head turning, body hemiclonic movements, or tonic-clonic convulsions.²¹ Post-TBI seizure activity may initially present as focal seizures that were previously classified as simple partial seizures where no loss of consciousness is exhibited, and only subjective symptoms are experienced by the individual during a seizure.²² Focal seizures may be identified by first observing an altered state of consciousness or by considering the patient's self-report of an internal experience. Sometimes a focal seizure may be a subtle movement or behavior that is difficult to differentiate, especially in animal research models.²¹ Recently established guidelines by the ILAE removed the differentiation between simple partial and complex partial seizures, but noted

that it is still clinically relevant to determine if seizure activity presents with impairment of consciousness/awareness or altered cognition.²² In documented case studies, researchers note that among individuals with TBI who experienced focal seizures (formerly described as complex partial seizures), they often have seizures that are refractory to many common anti-epileptic medications.²¹ The varied presentations of PTS make the task of diagnosing a seizure difficult for the clinical staff. It is very important to obtain a thorough history from the patient or caregiver about any specific post-traumatic symptoms. Obtaining this information can often be a challenging task due to the common occurrence of altered mental status, agitated behavior, and decreased awareness among individuals who have experienced a TBI.⁶ Important items to assess when diagnosing PTS include the signs and symptoms listed in Table 1 on Page 5.

Electroencephalogram (EEG) is a technique commonly used to aid in the diagnosis of seizures. Continuous EEG monitoring may be helpful in establishing a diagnosis when determining whether a patient has subclinical seizures or possibly non-convulsive status epilepticus. Additionally, clinicians may want to consider the use of video-EEG to help discriminate epileptic seizures from psychogenic nonepileptic seizures (PNES), conversion reaction, and nonepileptic paroxysmal episodes.²³

Prophylaxis and Treatment for PTE

Based on current clinical guidelines, clinicians are encouraged to prescribe prophylactic anti-epileptic drugs early in the hospital course for individuals with significant brain injury. Guidelines specify phenytoin for seven days post-injury; however, the recommendation for seizure prophylaxis comes from a study published in the *New England Journal of Medicine* in 1990.²⁴ Prior to 1990, the use of medications for seizure prophylaxis post-TBI was not widely practiced. The evidence regarding therapeutic levels of phenytoin suggests that different plasma concentration levels of phenytoin were associated with seizure prevention. Importantly, there was no benefit found in patients treated with phenytoin versus placebo in the development of late seizures.²⁵ However, there was a significant benefit in reducing the seizure rate by 73 percent within the first week after injury.^{24,25}

Prophylactic use of phenytoin is not without the possibility of adverse events. Common adverse reactions include rash, fevers, nystagmus, nausea, dizziness, leukopenia, leukocytosis, and lethargy.²⁶ Despite the treatment guidelines, many individuals with moderate to severe TBI receive daily prophylaxis with phenytoin well beyond the first seven days post-injury, and others who develop epilepsy may also be treated with phenytoin.¹⁹ Until recently, there has been little experimental literature examining the potential effects of phenytoin therapy on TBI pathology and recovery. However, recent studies show that prolonged phenytoin use after experimental TBI impairs learning and has adverse effects on neuroplastic markers and histological damage after CCI.¹⁹ These results provide multiple lines of evidence that ongoing phenytoin treatment can exacerbate tissue damage of hippocampal neurons and limit recovery after TBI, underscoring the fact that other treatment and prevention approaches are needed.

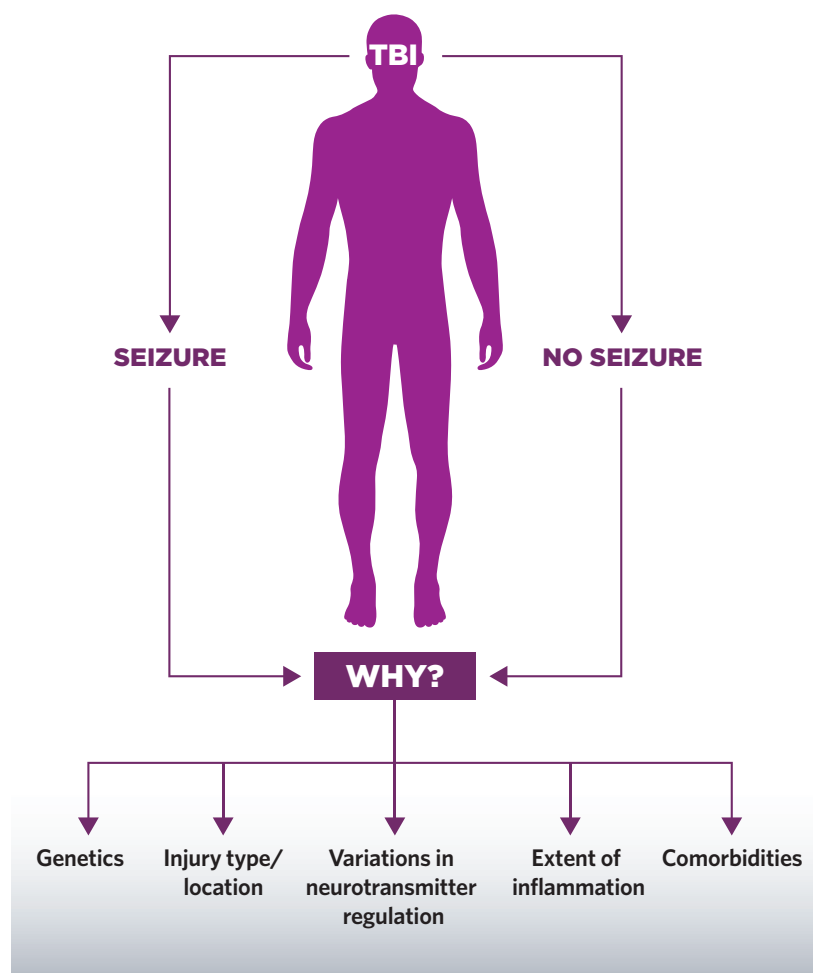


FIGURE 3: Interaction Among Personal Biology, Injury Mechanism, and PTE

TABLE 1: Potential Signs and Symptoms to Consider When Diagnosing PTE⁶

Premonitory aura — A warning symptom occurring before seizure activity begins
Episodes of altered awareness or unresponsiveness
Déjà vu — Recalling an event or visual image as if it already occurred when it is actually novel Jamais vu — A familiar encounter is being experienced as if it is novel to an individual when an individual has actually already been exposed to that encounter before
Involuntary focal motor activity (e.g., clonic movements, hand and orolimentary automatisms) — repetitive actions of the oral area of the body or swallow reflex that can include lipsmacking, chewing, or swallowing
Olfactory hallucinations
Gustatory hallucinations
Amnesia or periods of lost time
Unexplained nocturnal injuries or incontinence

In recent years, practitioners have utilized newer agents for both prophylaxis and treatment, despite limited to no evidence about treatment effects or mechanisms in the context of injury. Levetiracetam recently has been a popular agent largely due to its reported good safety and low side-effect profile. Practical considerations when analyzing the benefits of phenytoin versus levetiracetam include cost, since levetiracetam is more expensive than phenytoin. However, the side effect profile of levetiracetam is low, and it does not appear to adversely impact cognition. In contrast, phenytoin can adversely impact cognition, even in uninjured populations²⁷, and phenytoin has interactions with multiple other drugs requiring monitoring of serum levels for effectiveness or toxicity.

Daily treatment with levetiracetam had a significant beneficial effect on motor function and exploratory behavior, as well as a protective effect on hippocampal neuron sparing and in reducing contusion size.^{20,28} The findings also suggested that levetiracetam likely is neuroprotective after TBI due to its ability to reduce inflammation post-injury and normalize glutamate transporter expression.²⁸ Possibly due to these neuroprotective effects, one study reported that in patients who received prophylactic treatment with levetiracetam, they had lower disability rating scale (DRS) (better scores) and higher Glasgow Outcomes Scale-Extended (GOSE) (better scores) compared to

those treated with phenytoin.²⁹ While levetiracetam has many benefits, it does have some side effects. One study reported side effects such as somnolence (15%), fatigue (15%), minor infections (13%), and dizziness (9%).³⁰

It is important to develop an individualized treatment plan for each patient with PTE. Further consideration of the best known clinical agents for PTE is necessary. Possible therapies to consider when treating PTE are included in Table 2 on Page 6, along with each mode of action, dosage, metabolism, select drug-drug interactions, potential neurological side effects, and ancillary neurologic use. Drug selection may be guided, at least in part, by its effects on other symptoms and sequelae common to TBI. These types of clinical considerations also are particularly important when attempting to streamline drug utilization and minimize unwanted side-effects.

Clinical Outcome

For MB, physical medicine and rehabilitation consultation service recommended that valproate be discontinued and that the patient begin levetiracetam. After MB was on levetiracetam, his focus, attention, and energy-level improved. He was able to participate more actively with therapy approximately two days after starting levetiracetam. Importantly, he continued to be seizure-free. It was recommended that MB start a comprehensive inpatient brain injury rehabilitation program for additional therapy. While in therapy, MB's cognitive functioning gradually improved. He was able to participate in vestibular therapy. His continued therapy goals included returning to work as a mechanic, and he is attending therapy sessions with an occupational therapist to learn adaptive techniques. He also required additional therapy sessions with a neuropsychologist due to persistent anxiety from the accident manifested as restlessness and inability to concentrate. He is currently living in the community and continuing to improve his proficiency with activities as a mechanic. He has a job coach to assist him with returning to work. MB is 18 months post-TBI and has been free of seizures for 12 months.

TABLE 2: Potential Therapies to Consider for Management of PTE

Medication	Seizure Type	Mode of Action	Dosage*	Metabolism	Monitoring Levels (Yes/No)	Select Drug-Drug Interactions — Drug Effect**	Neurological Side Effects***	Ancillary Neurologic Use
Phenytoin (ex. Dilantin®)	Generalized tonic-clonic and complex focal (psychomotor and temporal lobe)	Voltage-activated Na ⁺ channels; GABA	100 mg PO TID; maintenance dose 300–400 mg/day (MAX dose 600 mg/day)	CYP-Hepatic	Yes — Therapeutic level: 10–20 mcg/mL	CYP450 inducer; Carbamazepine — decreases phenytoin concentration, phenytoin decreases carbamazepine concentration; benzodiazepines — variable; phenobarbital — variable	Depressed cognition, cerebellar-vestibular effects, and behavioral changes	Trigeminal and related neuralgias
Valproic Acid	Focal epileptic seizure; monotherapy, initial	Voltage-activated Na ⁺ channel; small reductions of T-type Ca ²⁺ currents	10–15 mg/kg/day PO (give in 2–3 divided doses if total daily dose exceeds 250 mg) (MAX dose 60 mg/kg/day or less with a therapeutic serum range of 50–100 mcg/mL)	CYP-Hepatic	Yes — Therapeutic level: 50–100 mcg/mL	Phenobarbital — increases phenobarbital concentrations, decreases valproic acid effectiveness; carbamazepine — increases carbamazepine concentrations and/or decreases valproic acid concentrations	Sedation, ataxia, and tremor	Mood instability; post-traumatic headaches
Carbamazepine (ex. Tegretol®)	Focal, generalized, and mixed types, initial	Voltage-activated Na ⁺ channels	200 mg PO BID for the first week, do not exceed 1200 mg/day	CYP-Hepatic	Yes — Therapeutic plasma level: 4–12 mcg/mL	Phenytoin — decreases phenytoin concentrations and/or decreases carbamazepine concentrations; phenobarbital — decreases carbamazepine exposure and potential loss of efficacy; levetiracetam — may lead to increased concentrations of carbamazepine; lamotrigine — may decrease lamotrigine effectiveness and may increase carbamazepine concentrations; fluoxetine — increased carbamazepine exposure and increased carbamazepine concentrations; zolpidem — decreased zolpidem plasma concentrations; alprazolam — may decrease alprazolam plasma levels	Stupor or coma, hyperirritability, convulsions, drowsiness, vertigo, and ataxia	Neuropathic pain; emotional lability
Levetiracetam (ex. Keppra®)	Focal seizure, (monotherapy); new diagnosis or focal seizure (adjunct therapy); myoclonic, tonic-clonic	No clear mechanism; synaptic vesicle protein SV2A implicated	Monotherapy: 500 mg PO Daily MAX dose 3000 mg/day; adjunct: 500 mg PO BID	Enzymatic hydrolysis; non-CYP inducer, not high-affinity substrate for CYP	No	Carbamazepine — may lead to increased concentrations of carbamazepine	Somnolence, asthenia, and dizziness	Motor restlessness
AUXILIARY								
Topiramate (ex. Topamax®)	Tonic-clonic seizure, primary generalized (initial monotherapy); focal seizure; tonic-clonic seizure primary generalized (adjunct therapy)	Voltage-gated Na ⁺ currents; GABA; glutamate; weak carbonic anhydrase inhibitor	Monotherapy: 25 mg PO BID (morning and evening); increase dose weekly by 25 mg PO BID (MAX dose), 200 mg PO BID; adjunct therapy: begin at 25–50 mg PO daily; may increase dosage by 25–50 mg/day at 1-week intervals—maintenance dose of 200–400 mg/day in 2 divided doses	Mainly renal; some hepatic	No	Phenobarbital — decreases topiramate concentrations; phenytoin — variable; valproic acid — decreases topiramate or valproic acid concentrations; carbamazepine — decreases topiramate concentrations; buprenorphine — may cause additive CNS or respiratory depression; citalopram — increased citalopram exposure and risk of QT interval prolongation	Somnolence, fatigue, weight loss, and nervousness	Headaches
Lamotrigine (ex. Lamictal®)	Focal seizure (monotherapy or adjunct therapy); tonic-clonic seizure, primary generalized (adjunct therapy)	Recombinant Na ⁺ channels; glutamate	Regimens containing inducers of lamotrigine (inducer-medication may increase the metabolism rate of lamotrigine and decrease the effect of lamotrigine; valproic acid or regimens not containing agents that induce or inhibit lamotrigine glucuronidation (inhibitor-medication may inhibit the metabolism of lamotrigine and cause too high of a level of lamotrigine to be in the system): first two weeks—25 mg PO Daily; weeks 3 and 4: 25 mg twice daily; week 5 and beyond: increase dose by 25–50 mg every 1–2 weeks (usual maintenance dose: 100–200 mg daily in 2 divided doses)	Hepatic	No	Valproic acid — increases lamotrigine concentrations, increase in valproic acid levels; carbamazepine — increase in carbamazepine concentrations and increases metabolism of lamotrigine; phenytoin — may decrease lamotrigine concentrations	Dizziness, ataxia	Mood instability
Gabapentin (ex. Neurontin®)	Focal seizure; adjunct	GABA	300 mg PO TID; usual MAX dose 2400 mg/day, may increase to 3600 mg/day for short duration in select patients	Not metabolized, excreted unchanged in urine	No	Morphine	Somnolence, dizziness, ataxia, and fatigue	Neuropathic pain

*Dosing based on immediate-release formulations. Please consult product insert for additional details.

**Drug-drug interactions list is not all encompassing.

***Neurologic side effects list is not all encompassing and does not include side effects in other organ systems.

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