A Systematic Appraisal of Neurosurgical Seizure Prophylaxis: Guidance for Critical Care Management

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Abstract: Clinical decisions are often made in the presence of some uncertainty. Health care should be based on a combination of scientific evidence, clinical experience, economics, patient value judgments, and preferences. Seizures are not uncommon following brain injury, surgical trauma, hemorrhage, altered brain metabolism, hypoxia, or ischemic events. The impact of seizures in the immediate aftermath of injury may be a prolonged intensive care stay or compounding of the primary injury. The aim of brain injury management is to limit the consequences of the secondary damage. The original intention of seizure prophylaxis was to limit the incidence of early-onset seizures. However, clinical trials have been equivocal on this point, and there is concern about the adverse effects of antiepileptic drug therapy. This review of the literature raises concerns regarding the arbitrary division of seizures into early onset (7 d) and late onset (8 d and beyond). In many cases it would appear that seizures present within 24 hours of the injury or after 7 days, which would be outside of the scope of current seizure prophylaxis guidance. There also does not appear to be a pathophysiological reason to divide brain injury–related seizures into these timeframes. Therefore, a solution to the conundrum is to reevaluate current practice. Prophylaxis could be offered to those receiving intensive care for the primary brain injury, where the impact of seizure would be detrimental to the management of the brain injury, or other clinical judgments where prophylaxis is prudent. Neurosurgical seizure management can then focus attention on which agent has the best adverse effect profile and the duration of therapy. The evidence seems to support levetiracetam as the most appropriate agent. Although previous reviews have identified an increase cost associated with the use of levetiracetam, current cost comparisons with phenytoin demonstrate a marginal price differential. The aim of this review is to assimilate the applicable literature regarding seizure prophylaxis. The final guidance is a forum upon which further clinical research could evaluate a new seizure prophylaxis paradigm.

Key Words: neurosurgery, seizures, prophylaxis, neurosurgical intensive care, phenytoin, levetiracetam, traumatic brain injury

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New-onset seizures are a well-documented complication of brain injury.[1] Seizures are described as immediate, early, or late if occurring within 1, 7, or >7 days, respectively, after the event that precipitated the seizure.

Precipitants of seizures include surgery for brain tumors, subarachnoid hemorrhage, anoxic brain injury, and traumatic brain injury. The prophylactic use of antiepileptic drugs (AEDs) following brain trauma has been a source of debate among specialist groups.[2–7] The proponents suggest that the routine use of prophylactic AEDs will decrease the incidence of early-onset seizures or minimize the risk of late-onset seizures.[8] It is also argued that seizures are likely to compromise recovery, although this has not been convincingly demonstrated.[9,10] The argument against is that as well as not having demonstrable benefit, antiepileptic prophylaxis leads to a number of adverse effects, particularly with regard to the most frequently used drug, phenytoin.

If the practice of prescribing prophylactic antiepileptic therapy in neurosurgery is to continue the issues to address are as follows:

Does a seizure compromise recovery?
Do all types of brain injury equally need antiseizure prophylaxis?
Which AED has a favorable adverse effect profile?
Is there an ideal dosing schedule?
Is there an acceptable duration for prophylaxis?

In recent years levetiracetam has received considerable interest as it may represent an improvement on the older drugs such as phenytoin, sodium valproate, phenobarbital, and carbamazepine. Levetiracetam does not interfere with the metabolism of other medications, it has limited adverse effects and a wide safety profile, it is available as an intravenous formulation, and has a wide safety profile and a flexible loading dose schedule.[11,12] Several studies, reports, and editorials have considered the application of levetiracetam for neurosurgical seizure prophylaxis.[12–22]

Recent meta-analyses of seizure prophylaxis following brain injury or following brain surgery have not

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demonstrated benefit.[1,3,5,23] However, a meta-analysis is limited in its scope as it is not able to assimilate the many clinical reports and expert opinions on the relative performance of levetiracetam for seizure prophylaxis.[23] A systematic review is able to analyze a broader range of evidence from audits, surveys, case reports, clinical trials, and expert opinion.

The aim of this review is to assimilate the available evidence and consider a pragmatic approach for clinicians managing critical care patients at risk of seizures. The final guidance will not be a robust Cochrane style review, but in the absence of clarity, and the continuity of the practice of seizure prophylaxis, a practical guide can inform debate, inspire discussion, and appraise further scientific research and clinical audit.

A HISTORY OF SEIZURE PROPHYLAXIS

The concept of 7-day seizure prophylaxis stems from descriptions of seizures following brain trauma in the early 20th century, particularly the First World War. Before this period, early pharmacological paradigms for seizure control involved potassium bromide and a variety of unethical nonpharmacological techniques of poor efficacy.[24,25] However, the management of seizures in this period needs to be placed in a social context, where subjects with epilepsy would be confined to the asylum or the workhouse. Prescribed methods to limit the onset of idiopathic seizures included an avoidance of corporal punishment, plenty of fresh air, and avoiding sexual indulgences.[24] Potassium bromide in 1857 and phenobarbital in 1912 offered the possibility of pharmacological seizure control.

The Franco-Prussian war (1870 to 1871) provided some material to describe the seizures that followed blunt or traumatic brain injury.[26] The enormous numbers of casualties from the use of mortars and machine guns in the First World War produced several large case series of epilepsy following traumatic brain injury.[26–29] Phenobarbital and bromide given for 2 years for the prevention of posttraumatic seizures following head injury was recommended at that time.[30]

Turner[26] in the First World War and Ascroft[31] in the Second World War published case series and differentiated between early-onset and late-onset seizures following brain trauma. The time scale used for the definition of early-onset seizures in these descriptions varied from 24 hours to several months.[32,33]

The Korean (1950 to 1953) and Vietnam Wars (1959 to 1975) brought fresh understanding of traumatic head injury.[34] The concept of early-onset seizures was clarified as being within 7 days of the injury and pharmacological prophylaxis was limited to phenytoin or phenobarbital. Rish and Caveness[35] reported that phenytoin prophylaxis used after combat injury in the Vietnam War was neither practical or desirable. In contrast, Servit and Musil,[36] in a retrospective audit recommended phenytoin or phenobarbital prophylaxis for 2 years after head injury. In 1973, a survey of neurosurgeons reported that only 58% of neurosurgeons in North America used seizure prophylaxis with either phenytoin or phenobarbital.[37] A survey in 2004 identified prophylaxis was practiced by 70% of North American neurosurgeons following brain tumor surgery, although this had been discouraged by the American Academy of Neurology in 2000.[2,38] A variety of clinical trials have both supported and refuted the benefit of phenytoin in reducing early-onset seizures.[10,39,40] Reviews of the literature by Temkin and a Cochrane review (2001), the American Academy of Neurology (2003) the American Brain Trauma Foundation (2007) concluded that phenytoin and/or sodium valproate were of benefit for the prophylaxis of early-onset seizures after traumatic brain injury.[1,3,41,42] Although a reduction in early seizures may be observed, the mortality appears unaffected by seizure prophylaxis.[1,39] However, many clinicians have become concerned that phenytoin compromises functional recovery from traumatic brain injury.[43,44] Similar concerns about the adverse effects from prophylactic phenytoin have been observed in trials following brain tumor resection and subarachnoid hemorrhage.[45–47]

The 1980s saw the introduction of carbamazepine and sodium valproate. In a meta-analysis of seizure prophylaxis, Temkin observed that with regard to phenytoin, carbamazepine, sodium valproate, and phenobarbital,[42,48,49] the data regarding traumatic brain injury was of poor quality or small sample size and there was limited evidence to confirm or refute their benefit.[35,50] There are no English-language studies of seizure prophylaxis with carbamazepine, although 1 study has demonstrated the negative cognitive effects of carbamazepine after head injury.[51] A study of sodium valproate for the prophylaxis of seizures following intracerebral hemorrhage, concluded that there was "no statistically significance difference in early or late seizures" between sodium valproate and placebo groups, although a trend toward less seizures was observed in those who received sodium valproate.[52] Temkin, in a trial of phenytoin or valproate in traumatic brain injury concluded that "Valproate therapy shows no benefit over short-term phenytoin therapy for prevention of early seizures."[53]

Since 2009, a variety of new AEDs have become available. However, apart from levetiracetam, there are no human clinical trials available that have observed their effect following traumatic brain injury, lacosamide and lamotrigine are available as intravenous preparations and may be a suitable alternative to phenytoin or levetiracetam when these are contraindicated or seizure control is unsuccessful.

POSTTRAUMATIC SEIZURES: IMPACT AND OUTCOME

Following trauma, the brain is vulnerable to secondary insults that may worsen the injury and the resultant outcome. These include hypoxia, hypotension, altered glucose, and oxidative metabolism and elevated intracranial pressure. Seizures may promote many neurochemical perturbations that may compound the

primary brain injury. There is clinical evidence to both support,[54–62] and refute[63–65] this concept. The argument that seizures compromise brain function is more compelling and persuasive when balanced against the clinical compromise that might occur through failing to act.

LITERATURE SEARCH METHODS

The Great War generated several descriptions of early and late posttraumatic seizures. From these early reports, the concept of 7-day prophylaxis schedules could be said to originate. The literature search therefore considered relevant articles from 1900 to January 2015. Examination of the scientific literature used MEDLINE (1900 to January 2015), Embase (1947 to January 2015), CINAHL (1937 to January 2015), and the Cochrane database followed up with a subsequent manual review of article bibliographies. Original English-language documents were traced using the following key words: *Neurosurgery* and *seizure prophylaxis* combined with *phenytoin*, *carbamazepine*, *sodium valproate*, *phenobarbital*, *gabapentin*, *lamotrigine*, *topiramate*, and *levetiracetam*. The review also considered specific causes of brain injury that lead to seizures (subarachnoid hemorrhage, traumatic brain injury, stroke, intracerebral hemorrhage, anoxic brain injury, brain abscess, and brain tumors). For each publication, the abstract was first examined. Inclusion required that the study involved human subjects and the full manuscript was published in English. Original research was included. Review articles and expert opinion were also considered.

SEIZURE PROPHYLAXIS: PHARMACOLOGY

The prevention or control of seizures following brain injury is the prima facie role of an AED used for seizure prophylaxis. The ideal AED should have a broad spectrum of activity against a wide variety of seizure types and an absence of adverse side effects, or at least an acceptable safety profile with respect to pharmacokinetic and pharmacodynamic factors.[66] Desirable kinetic characteristics include once daily dosing, an absence of active metabolites and an absence of drug interactions or idiosyncratic effects. Alongside these ideal characteristics, the availability of intravenous and oral formulations is essential. Phenytoin departs from these ideal goals, but the new AEDs, particularly levetiracetam have more acceptable profiles.

LEVETIRACETAM: PHARMACOLOGY

Levetiracetam, a 2S-(2-oxo-1-pyrrolidinyl) butanamide, is a nonaromatic, antiepileptic agent, with a novel mechanism of action.[67] The synaptic vesicle protein SV2a is the unique brain binding site for levetiracetam.[68] The binding to SV2a provides an antiepileptic profile for levetiracetam that is unique among the AEDs.[69] It is not clear how the binding of SV2a leads to the suppression of seizure activity, but the potential for levetiracetam to limit epileptogenesis is being explored.[70,71]

Levetiracetam is available as an oral formulation, with almost 100% bioavailability.[72] Because of its complete and linear absorption, plasma levels can be predicted from the oral dose of levetiracetam expressed as mg/kg body weight. Therefore, plasma monitoring of levetiracetam is not required in normal circumstances.

Food lowers the peak plasma concentration, but does not reduce the bioavailability. The serum half-life is 5 to 8 hours and is extended with increasing age and reduced creatinine clearance[73,74] (Table 1). No significant drug interactions have been reported and most of the drug is excreted unchanged in the urine.[73] The limited hepatic metabolism is not dependent on cytochrome p450. Levetiracetam has low protein binding, can be given without a break in oral feeding, and its short half-life leads to steady state levels within 2 days.[73] The kinetic variables and sustained cerebrospinal fluid levels support twice daily oral administration.[72,75] Dosing studies recommend 500 to 1000 mg twice daily, but because of its wide safety profile doses up to 4000 mg/d can be considered.

Dosage reductions should be considered for patients with renal impairment.[73] The clearance is enhanced by dialysis and the dose of levetiracetam should be increased by 30% to 50% during continuous dialysis, or a supplemental dose of 250 to 500 mg after intermittent dialysis. In the presence of hepatic impairment, dosage adjustments are not necessary.[73] Where hepatic failure has been precipitated by other AEDs, levetiracetam is a safe alternative.[76]

Regarding drug interactions, coadministration of levetiracetam does not affect oral contraception, warfarin, sodium valproate, carbamazepine, phenytoin, lamotrigine, or any of the other AED.[73] Plasma monitoring is not recommended at present, although an effective plasma level is 80 to 270 mmol/L.[73]

The adverse event profile includes somnolence, asthenia, headache, and an increase in the reporting of the common cold and upper respiratory tract infections[72,77–80] (Table 2). The safety profile of levetiracetam has been tested with doses in excess of recommended, up to 100 mg/kg/d, without serious adverse events.[11,81] When required, intravenous loading of 1000 mg intravenously may be safely administered over 15 minutes.[11]

TABLE 1. Dosing Adjustment for Adult and Adolescents Patients Weighing >50 kg With Impaired Renal Function

Groups	Creatinine Clearance (mL/min/1.73 m^2)	Dose and Frequency
Normal	> 80	500 to 1500 mg twice daily
Mild	50-79	500 to 1000 mg twice daily
Moderate	30-49	250 to 750 mg twice daily
Severe	< 30	250 to 500 mg twice daily
End-stage renal disease patients undergoing dialysis		500 to 1000 mg once daily

In the presence of end-stage renal disease and dialysis, a 750 mg loading dose is recommended on the first day of treatment with levetiracetam. After dialysis, a 250 to 500 mg supplemental dose is recommended.

TABLE 2. Adverse Events in Patients Taking Antiepileptic Agents

Reported Complications					Physiological and Pharmacological Systems
Levetiracetam	**Phenytoin**	**Carbamazepine**	**Sodium Valproate**	**Phenobarbitone**	
Anger, delirium, dizziness, somnolence, fatigue, headache	Memory impairment and intellectual decline, horizontal gaze nystagmus, cerebellar ataxia	Cognitive compromise	Cognitive compromise	Somnolence, dizziness/vertigo, diplopia, nystagmus, blurred vision, ataxia, chorea and dystonia, tremor, habit forming	Neurological
None reported	Hypotension, bradycardia, other arrhythmias	Arrhythmias, hypertension or hypotension, bradycardia	Hypertension, hypotension, palpitations	Hypotension	Cardiovascular
Very rare reports of hepatoxicity, often in association with other antiepileptic agents	Hepatic derangements	Cholestasis	Severe hepatitis	Liver damage	Hepatic
No kinetic drug interactions and linear kinetics at doses of 500-5000 mg/d. Age effects clearance	Zero-order kinetics at high drug concentrations with unpredictable plasma levels, induces p450 enzymes with associated drug interactions, with nimodipine and chemotherapeutic agents	A potent inducer of cytochrome P450	Hepatic enzyme inhibitor and may interfere with the metabolism of other agents	Hepatic enzyme inducer and interferes with the metabolism of other antiepilpetic agents	Pharmacological
None reported	Pruritis, hirsutism, and coarsening of facial features, drug-induced lupus, Stevens Johnson syndrome, toxic epidermal necrolysis	Stevens Johnson syndrome, toxic epidermal necrolysis, exanthema, alopecia	Alopecia, discoid lupus erythematosus, maculopapular rash	Angioedema, exfoliative dermatitis, fever	Dermatological
Very low or no associated malformation rates	Teratogenic	Teratogenic	Teratogenic	Teratogenic	Pregnancy and teratogenic effects
No effect	Alteration in kinetics of chemotherapeutic agents	Alteration in kinetics of chemotherapeutic agents	Alteration in kinetics of chemotherapeutic agents	Alteration in kinetics of chemotherapeutic agents	Chemotherapy
No effect	Skin lesions and erythema multiforme particularly associated with cranial irradiation	Mitigation and protection against ionizing radiation	May be neuroprotective during cranial irradiation	Erythema multiforme associated with cranial irradiation	Radiotherapy
Minimal or no effect	Macrocytic anemia, leukopenia	Thrombocytopenia, aplastic anemia, leukopenia	Abnormalities of coagulation	Thrombocytopenia, megaloblastic anemia	Hematology
No association with anticonvulsant hypersensitivity syndrome	Anticonvulsant hypersensitivity syndrome including hepatitis, myocarditis, lympheodema	Syndrome of inappropriate antidiuretic hormone secretion	Hyperammonemia, hair loss, weight gain	Rickets, contraindicated in patients with porphyria	Other

Complications reported with levetiracetam are reported less frequently than those of other antiepileptic agents.

LEVETIRACETAM MONITORING

It is recognized that the desired therapeutic effect of many AEDs is achieved within a specific range of serum concentrations with lower concentrations less likely to produce a reduction in seizures and high concentrations likely to be associated with adverse effects. The concentration range most frequently effective is called the reference range. However, therapeutic effect may be achieved below the reference range and toxic effects may be present within the reference range.[82] The interpretation of a serum concentration needs to be considered within the clinical context. Indeed, clinical trials have not demonstrated that seizure management is more effective when clinicians use AED therapeutic monitoring. Within the context of neurosurgical seizure prophylaxis for neurosurgery, high-dose therapy is to be preferred to achieve serum concentrations that can prevent seizures. During short course levetiracetam therapy, therapeutic drug monitoring may be unhelpful in the absence of seizures.

If breakthrough seizures do occur, therapeutic sampling should be considered. Blood samples should be performed at steady state or after 4 to 5 half-lives. For levetiracetam, this is 1 to 2 days with the reference range of 12 to 46 mg/L (70 to 270 μmol/L).[82] In the presence of seizures, the total levetiracetam dose can be increased, the frequency

of dosing can be increased, or second-line and third-line therapy may be advocated. This is considered under the "Seizure prophylaxis and escalation therapy" section.

EEG MONITORING

It is estimated that up to 50% of patients in coma following a brain injury may develop seizures, and many are nonconvulsive.[83] Nonconvulsive seizures appear in a relatively high percentage of comatose patients without any clinical signs of seizure activity. Both convulsive and nonconvulsive seizures will lead to neuronal damage if control is delayed. A single EEG will detect 50% of nonconvulsive seizures. The diagnostic yield is improved with the application of continuous EEG (cEEG) monitoring. In a small case series of patients presenting with status epilepticus, Kaplan detected all cases with Non Convulsive Status Epilepticus only after 3 to 5 days of cEEG monitoring.[84,85] Clinical trials have realized the value of cEEG monitoring for both detection of seizures, monitoring of AED therapy, and prognostication, with a reduction in morbidity and mortality.[86,87]

SEIZURE PROPHYLAXIS FOR NEUROSURGERY

The incidence of seizures following neurosurgery varies from 2% to 68% depending upon the precipitating cause (Table 3). The prophylactic administration of antiepileptic medication is commonplace in neurosurgical practice despite a lack of supporting evidence.[38]

The effect of AEDs has been studied following craniotomy and other neurosurgical conditions. North et al[88] observed a reduction in all seizures following craniotomy with phenytoin, but not of early-onset seizures. In contrast, Lee observed a reduction in early post-craniotomy seizures following a short course of phenytoin.[89] Temkin and colleagues concluded that seizure prophylaxis was justified for 1 week after surgery where the incidence of seizures was reduced by 40% to 50% and most evidence supported the use of phenytoin.[40,48] Ramakrishnan et al,[90] however, observed time to first seizure was on average between 5 and 8 days for subjects with traumatic brain injury following a craniotomy or craniectomy. Phenytoin was generally given as a single intravenous loading dose, then daily AED prophylaxis was stopped at 1 week, unless otherwise indicated.

Seizures are frequently associated with brain tumors, and prophylaxis may need to be continued for several months. Maschio and colleagues observed the effects of levetiracetam monotherapy on seizure control in patients with brain tumour–related epilepsy. During chemotherapy or radiotherapy, the majority of side effects were mild with a case of severe restlessness requiring discontinuation of levetiracetam.[91,92] de Santis et al[93] observed no reduction in seizures from 7-day phenytoin prophylaxis following resection of intracranial tumors. Phenytoin is associated with many adverse effects in combination with chemotherapy and radiotherapy (see "Seizure prophylaxis and hypersensitivity" section).

Beenen et al[94] observed no difference between prophylactic phenytoin and sodium valproate following various intracranial procedures, although the incidence of adverse effects was higher with phenytoin. Foy et al[95] showed no difference between carbamazepine and phenytoin following intracranial surgery, but the incidence of seizures and adverse effects was high in both the groups.

The evidence supporting the administration of prophylactic AEDs following subarachnoid hemorrhage is conflicting with advice supporting or refuting the practice.[96–98] The risk of seizures following coil embolization is lower than that follows surgical clip placement. Delayed cerebral ischemia, subdural hematoma, and middle cerebral artery aneurysms are secondary proseizure risk factors.[99,100]

Early seizures complicate up to 40% of intracerebral hemorrhages or infarcts.[101–103] Clinical trials either support or refute the benefits of prophylactic AEDs.[64,104–107] As patients with stroke are likely to be elderly, with end-organ dysfunction and taking multiple medications, levetiracetam may be more appropriate.[108,109]

Seizures complicate a brain abscess in around 40% of cases, although it can be up to 95%.[110,111] Phenytoin is most frequently described to manage early seizures,

TABLE 3. The Data for the Risk of Seizures is Taken From Various Sources

Pathology	Incidence of Early-onset Seizure (1-7 d) (%)	Evidence to Support Seizure Prophylaxis
Traumatic brain injury	3-21	No
Cerebral neoplasms (with or without surgery)	37-87	Yes
Craniotomy (nontrauma)	No data available	No
Subarachnoid hemorrhage	1.3-11	No
Intracerebral bleed	6.5-13	No
Anoxia/ischemia	30	Yes
Stroke	3-67	Yes
Intracerebral abscess	21-98	Yes
Meningitis/encephalitis	3-22	No
First unprovoked seizures	4.1-4.6	No
Late seizures after first unprovoked seizure	40-56	Yes

Cerebral neoplasms, cerebral abscess, stroke, and anoxia/ischemia damage appear to carry the highest risk and treatment may be considered. The risk of early-onset seizures is low following brain trauma and the benefit of early-onset seizure prophylaxis may not be balanced by the adverse effects.

however, the qualitative aspects of seizure control have not been considered.[110,112]

Where postoperative radiotherapy is used for brain tumors, phenytoin, phenobarbitone, and valproate are best avoided, after reports of unpredictable allergic-type skin reactions.[113]

Seizures are also common after cardiac arrest, and although they are an independent predictor of outcome, there is no guidance or clinical data supporting the use of prophylactic AEDs.[114,115]

SEIZURE PROPHYLAXIS IN CRITICAL CARE

Seizures in critical care present diagnostic challenges. Tonic-clonic movements may be absent, and somnolence, agitation, hypertension, tachycardia, and fever may be the presenting signs. These signs are not specific to seizures, indeed a visual reference to the presence of seizures is not guaranteed. Therefore, the use of continuous or daily EEG monitoring should be considered when consciousness is compromised through pharmacological coma or the presence of brain trauma.

Prophylactic seizure management of the critical care patient following brain trauma can present difficulties achieving therapeutic drug concentrations of AEDs.[116] Drug kinetics will be altered as a consequence of impaired drug metabolism, deliberate hypothermia, changes in acid/base status, renal dysfunction or augmented renal clearance, hepatic dysfunction, changes in cardiac output and in the volume of distribution, altered albumin concentrations, and the use of extracorporeal circulation.[117–119] How these factors will interact in the critical care patient is not easy to determine. Drug elimination will vary with changes in weight, height, age, body surface area, and creatinine clearance.[120] These alterations in drug kinetics have the potential to compromise the clinical effect or compound the toxic effects of AEDs. For example, therapeutic drug monitoring of phenytoin has demonstrated a wide variation in drug concentrations.[121] Comparing phenytoin and levetiracetam, adverse events in neurosurgical critical care are fewer with levetiracetam.[20] Levetiracetam does not interfere with the metabolism of other concomitantly administered drugs.

The availability of an intravenous formulation and a short half-life enables the administration of a loading dose and maintenance, if the oral route is compromised. Levetiracetam dose adjustments are necessary to accommodate the dilutional effect of an elevation in body water, faster systemic clearance, and a reduced half-life.[122] A total of 1.5 to 2 g twice daily are likely to realize effective plasma levels.

In the presence of mild, moderate, or severe renal impairment, dose adjustments are necessary.[123] Given the wide therapeutic index of levetiracetam (70 to 270 μmol/L), in contrast to phenytoin (20 to 80 μmol/L), therapeutic drug monitoring is not recommended.[121,124]

SEIZURE PROPHYLAXIS AS MONOTHERAPY

A consideration when using levetiracetam for seizure prophylaxis is that it is effective against seizures when used as a sole agent or monotherapy. Monotherapy has the benefit of reduced adverse effects when compared with polytherapy.[125] In 2006, a license extension allowed levetiracetam to be used as monotherapy for the treatment of partial-onset seizures.[126] Studies and audits have demonstrated good seizure control with 1000 to 3000 mg daily in many patients. Comparison with other AEDs demonstrates an equitable incidence of seizure control, with 50% of patients' seizure free within 1 year of starting therapy. Participant withdrawal from levetiracetam, as a result of adverse effects, is low compared with other AEDs.

SEIZURE PROPHYLAXIS AND PREGNANCY

Although the need for provision of both neurosurgical and seizure management services to pregnant patients is infrequent, no guidance is available to the intensive care physician. Many AEDs are known to be teratogenic and the fetus exposed to AEDs in utero is at risk from prematurity, low birth weight, increased fetal and neonatal death, congenital malformations, and developmental delay. Recent publications from UK, Australian, North American, and International pregnancy registers suggest that levetiracetam is not associated with teratogenic effects above the background observations.[127–130] No other publication has identified a teratogenic effect. The advice from the manufacturer of Keppra (UCB Pharma Ltd., Brussels, Belgium) is that levetiracetam should not be used in pregnancy (UCB Pharma Ltd., personal written communication, 2014). The simple kinetics of levetiracetam makes dose adjustments in pregnancy easier than lamotrigine, phenytoin, sodium valproate, and carbamazepine.

There are limited data regarding dose schedules for levetiracetam in pregnancy, but clinical reports demonstrate an increase in the renal clearance and the volume of distribution with a decline in the plasma concentration of up to 50%, particularly in the third trimester.[131–135] A doubling of the levetiracetam dose should be considered by the third trimester. However, plasma monitoring is advised as accurate predictions are not available, and exceeding therapeutic levels (70 to 270 μmol/L) can lead to severe behavioral disorders.[131,133,136,137] Case reports also suggest that an increase in the frequency of dosing can reduce breakthrough seizures in the third trimester without an increase in the daily dose.[137] The fall in serum levels following in the third trimester, is followed by a rapid rise in the serum concentration of levetiracetam after delivery.[135]

Sodium valproate is to be avoided during pregnancy because of the known cognitive effects on child language and motor skills.[138] The risk is further enhanced with higher AED dosages, higher AED serum levels, and polytherapy. The use of folate supplements and treatment with vitamin K at birth and possibly the mother late in pregnancy is recommended for AEDs prescribed that interfere with vitamin K (carbamazepine, phenobarbitone, and topiramate).

SEIZURE PROPHYLAXIS AND ESCALATION THERAPY

In the event of breakthrough seizures, consideration needs to be given to the appropriate second-line and third-line therapy beyond levetiracetam. The acute management of a seizure can follow national guidelines, but seizures following brain trauma or tumors may be difficult to control.[139] An audit of second and third-line AEDs in patients with brain tumors recommended pregabalin, levetiracetam, lamotrigine, gabapentin, valproic acid, and phenytoin. However, referral to a neurologist with experience in the management of provoked seizures (seizures where a structural or metabolic insult to the brain is responsible for the seizure) should be considered. If chemotherapy is envisaged, it is recommended that enzyme inducing agents are avoided to limit clinical adverse drug interactions.[140] Where radiotherapy is planned, phenytoin should be avoided, given the risk of hypersensitivity reactions.

SEIZURE PROPHYLAXIS AND COGNITIVE FUNCTION

Through the interaction with ion channels, metabolic enzymes, neurotransmitter receptors, and transporters in the brain, AEDs are able to limit or stop the propagation of seizure activity. These effects may also compromise brain activity and present as cognitive impairment, fatigue, somnolence, ataxia, asthenia, nystagmus, tremor, and mood disturbance. Adverse cognitive effects may manifest as impaired attention, vigilance, psychomotor speed, and memory.[141] Multiple factors can affect cognition following cerebral trauma and seizures; phenytoin and carbamazepine may compound the cognitive deficits of the brain injury and compromise recovery.[44]

Phenytoin has been demonstrated to impair cognitive recovery after traumatic brain injury,[51,142] whereas neither phenytoin nor sodium valproate has been shown to compromise cognitive recovery after craniotomy.[94] The cognitive impact of AED prophylaxis on patients with brain tumors is affected by other factors such as tumor progression, surgery, seizure burden, and combination AED therapy.[143] Some observers have reported no cognitive decline with sodium valproate and levetiracetam combination therapy, whereas others have reported a variety of negative cognitive effects with both older and new type AEDs.[144–146]

Following intracerebral hemorrhage, patients receiving levetiracetam had improved cognition at discharge when compared with those subjects receiving phenytoin.[16,44] Studies of the older AEDs, carbamazepine, phenytoin, phenobarbital, and sodium valproate have not observed consistent declines in cognitive function when applied to healthy volunteers or subjects with epilepsy.[147–153] Studies observing cognitive and behavioral effects of levetiracetam have reported a low level of these effects, particularly depression, nervousness, anxiety, hostility, and emotional lability.[154–157]

SEIZURE PROPHYLAXIS AND HYPERSENSITIVITY

AEDs have been recognized as among the most common medications associated with cutaneous adverse reactions. These reactions may appear within a week of commencing the agent and may resolve with cessation of therapy.[158] Some reactions are severe, life threatening, and systemic. These reactions may form part of a spectrum of conditions such as Stevens Johnson syndrome, toxic epidermal necrolysis, antiepileptic hypersensitivity syndrome, and drug reaction with eosinophilia and systemic symptoms. Cutaneous reactions may combine with systemic manifestations including fever, lymphadenopathy, malaise, hepatitis, nephritis, blood dyscrasias, and colitis.[159] These complications may be mild or be a morbid precursor.[160] The incidence of these conditions vary from 10% with lamotrigine and phenytoin to $<1\%$ with levetiracetam.[161] The incidence varies with agents, with reactions to the aromatic AEDs (phenytoin, lamotrigine, phenobarbital, carbamazepine) being more common when compared with the nonaromatic AEDs (sodium valproate, tiagabine, gabapentin, topiramate and levetiracetam).[162] The risk of an adverse reaction is increased with the use of >1 agent, a previous history of skin reactions, concomitant use of sodium valproate and lamotrigine, and certain genetic phenotypes.[159]

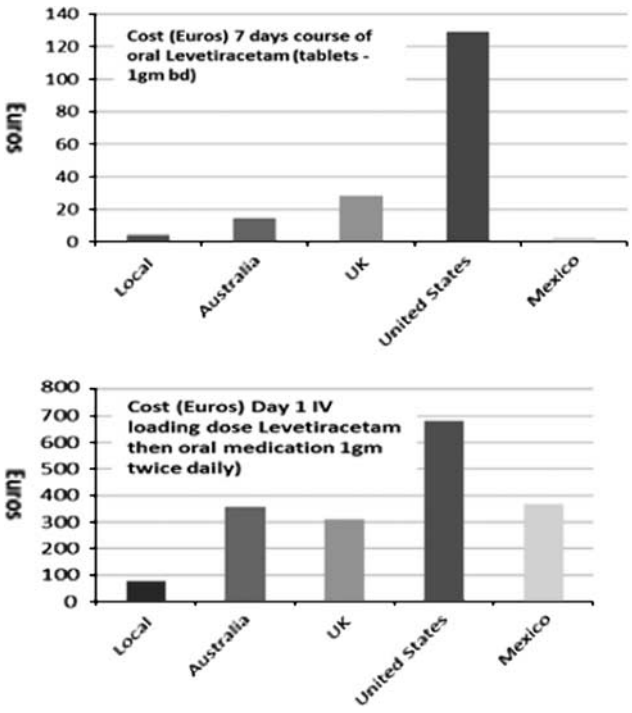
Erythema multiforme is associated with cranial irradiation for intracranial malignancy and coadministration of phenytoin. The description of phenytoin cutaneous reactions in this context has been proscribed its own pneumonic (EMPACT: erythema multiforme associated with phenytoin and cranial radiation therapy), and can be fatal in some cases.[163] Onset is typically within a few weeks of the start of phenytoin therapy.[39] Erythema multiforme and other cutaneous skin reaction are also described in association with levetiracetam, phenobarbital, lamotrigine, and carbamazepine with a lower frequency of reports that may reflect the incidence of prescribing.[164–167] Alhough cutaneous skin reactions are uncommon with levetiracetam, reports of other cutaneous reactions, such as urticarial vasculitis, are appearing in the literature.[168] As levetiracetam becomes the agent more often provided for seizure prophylaxis, the incidence of these infrequent complications may increase.

SEIZURE PROPHYLAXIS AND ECONOMICS

A health technology assessment of the cost effectiveness of AED treatment for seizures found that "There was little good-quality evidence from clinical trials to support the use of newer monotherapy or adjunctive therapy AEDs over older drugs, or to support the use of one newer AED in preference to another."[169] However, this review did not consider the evidence for short-term seizure prophylaxis in neurosurgery. Kazerooni and Bounthavong[170] and Pieracci et al[171] compared levetiracetam and phenytoin for the short-term prophylaxis of seizures in critical care. These studies demonstrated that levetiracetam offered benefits through a reduction in length of stay, reduced plasma monitoring costs, and a

TABLE 4. A Price Comparison of Phenytoin and Levetiracetam for the Prophylaxis of Seizures in Neurosurgery

Dosing Regimen	Cost of Early Seizure Prophylaxis From Local Pricing (€)	Cost of Keppra (UCB Pharma Ltd.) (€)			
		Australia	United Kingdom	United States of America	Mexico
Day 1-7 intravenous phenytoin	44.19				
7-d course of phenytoin oral suspension at 300 mg	3.99				
7-d course of phenytoin oral capsules at 300 mg	25.09				
Day 1 IV loading dose levetiracetam then oral medication 1 g twice daily	79.26	357.58	310.80	681.66	367.08
Day 1-7 with intravenous levetiracetam (1 g bid)	529.83	5006.12	4351.20	9543.24	5139.12
7-d course of oral levetiracetam (solution 1 g bid)	92.88	28.06	38.06	124.18	33.76
7-d course of oral levetiracetam (tablets—1 g bid)	4.17	14.28	28.00	128.80	2.41



The price data for levetiraacetam was taken from 2 sources. The local data were taken from data held in Sheffield Teaching Hospitals Trust pharmacy department. The data for the cost of Keppra in the United Kingdom, Australia, United States of America, and Mexico was provided by UCB Pharma Ltd. in May 2014. No international comparable cost data are provided for phenytoin. Graphs inset demonstrate cost differential between the countries illustrated graphically.

lesser impact of cognitive dysfunction when compared with phenytoin. Kazerooni and Bounthavong and Pieracci and colleagues concluded, respectively, that levetiracetam was or was not cost effective when compared with phenytoin. These 2 studies used twice daily intravenous levetiracetam in the models analyzed. Given the favorable kinetics of oral levetiracetam, it is practical and cost effective to use an oral formulation. Therefore, an analysis of the cost differential of prophylaxis with oral levetiracetam or phenytoin is now marginal (Table 4). The table illustrates that the direct costs of oral levetiracetam (£3.40) against oral phenytoin (£3.22) are marginal.[171] The economics of levetiracetam will vary between and within countries, and the economics of levetiracetam can be estimated.

SEIZURE PROPHYLAXIS: DURATION OF TREATMENT

The occurrence of seizures may follow any critical event involving injury to the brain.[172] Current descriptions of seizures following brain injury describe early-onset (0 to 7 d) and late-onset seizures (8 d or more). This division is entirely arbitrary and was used in descriptions of posttraumatic seizures during the First World War, with subsequent wars building on this concept of early-onset seizures.[173] Jennett and Lewin in 1960 clarified that early-onset seizures were those presenting within 7 days of a head injury.[174] Following this arbitrary divide, the concept of early and late seizures developed and has defined many studies of seizure prophylaxis. A review of published literature regarding a timeline for the onset of seizures suggests that in many studies that

TABLE 5. The Incidence of Immediate and Early Onset Seizures Following Brain Injury

Title of Study	First Author	Year of Publication	Total Number of Subjects Enrolled in Study	Presenting Pathology	Number of subjects Presenting with Seizures within 24 hours (%)	Numbers of subjects presenting with seizures between 1 - 7 days (%)	Numbers of subjects presenting with early onset seizures: No time provided (%)
Epilepsy and brain abscess[110]	Kilpatrick C	1997	34	Abscess	1 (2)	9 (25)	
Epilepsy Following Brain Abscess[111]	Koszewski K	1991	108	Abscess	N/A	N/A	37 (34)
Late seizures and morbidity after subdural empyema[175]	Cowie R	1983	89	Abscess	N/A	N/A	56 (63)
Predictors and long-term outcome of seizures after bacterial brain abscess[176]	Chuang M	2010	205	Abscess	N/A	N/A	27 (13)
The significance of seizures and other predictive factors during the acute illness for the long-term outcome after bacterial meningitis[177]	Wang, K-W	2005	117	Meningitis	25 (21)	N/A	
Seizures after Spontaneous Supratentorial Intracerebral Hemorrhage[64]	Passero S	2002	761	Intracerebral Haemorrhage	32 (4.2)	N/A	
Seizures after Spontaneous Intracerebral Hemorrhage[105]	Kwang-Moo W	2012	263	Intracerebral Haemorrhage	3 (0.3)	9 (1.2)	
The prophylactic use of an antiepileptic drug in intracerebral hemorrhage[104]	Reddig RT	2011	157	Intracerebral Haemorrhage	N/A	N/A	12 (7.6)
Seizures in Acute Stroke: Incidence, Risk Factors and Prognosis[178]	Procaccianti G	2012	2053	Stroke	39 (1.8)	27 (1.3)	
Seizures in Acute Stroke: Predictors and Prognostic Significance: The Copenhagen Stroke Study[179]	Reith J	1997	1197	Stroke	33 (2.7)	N/A	
Postinfarction Seizures A Clinical Study[180]	Gupta SR	1988	90	Stroke	27 (90)	3 (10)	
Population-based study of seizure disorders after cerebral infarction[181]	So EL	1988	535	Stroke	28 (85)	5 (15)	
The frequency, characteristics and prognosis of epileptic seizures at the onset of stroke[182]	Shinton RA	1988	230	Stroke	N/A	N/A	13 (5.7%)
Seizures after stroke a prospective multicentre study[183]	Bladin CF	2000	1897	Stroke	229 (75)	78 (25)	
Early and late seizures after cryptogenic stroke in young adults[184]	Lamy C.	2003	581	Stroke	10 (71)	4 (21)	
Prevalence and predictors of early seizure and status epilepticus after first stroke[185]	Labovitz DL	2001	904	Stroke	32 (86)	5 (14)	
Incidence and predictors of acute symptomatic seizures after stroke[186]	Beghi E.	2011	714	Stroke	33 (73)	12 (27)	
Anticonvulsant Use and Outcomes After Intracerebral Hemorrhage[106]	Naidech, AM	2009	98	Stroke	5 (5)	2 (2)	
Unruptured intracranial aneurysms: seizures and antiepileptic drug treatment following surgery[187]	Rabinowicz, AL	1991	21	Sub Arachnoid Haemorrhage	0	1 (5)	
The efficacy of antiepileptic drug prophylaxis in the prevention of early and late seizures following repair of intracranial aneurysms[188]	Raper, DMS	2011	259	Sub Arachnoid Haemorrhage	N/A	N/A	7 (2.7)
Seizures and Epilepsy following Aneurysmal Subarachnoid Hemorrhage : Incidence and Risk Factors[189]	Choi, KS	2009	547	Sub Arachnoid Haemorrhage	43 (8)	6 (1)	
Seizures after aneurysmal subarachnoid hemorrhage treated with coil embolization[190]	Byrne, JV	2003	243	Sub Arachnoid Haemorrhage	26 (11)	7 (3)	
	Lin, Y-J	2008	137	Sub Arachnoid Haemorrhage	5 (3.4)	8 (5.8)	

TABLE 5. (*continued*)

Title of Study	First Author	Year of Publication	Total Number of Subjects Enrolled in Study	Presenting Pathology	Number of subjects Presenting with Seizures within 24 hours (%)	Numbers of subjects presenting with seizures between 1 - 7 days (%)	Numbers of subjects presenting with early onset seizures: No time provided (%)
Risk factors and outcome of seizures after spontaneous aneurysmal subarachnoid hemorrhage[191]							
Epilepsy after craniotomy for intracranial aneurysm[192]	Fabinyi, GC and Artiola-Fortuny	1980	199	Sub Arachnoid Haemorrhage	4 (2)	5 (2.5)	
Characterization of perioperative seizures and epilepsy following aneurysmal subarachnoid hemorrhage[193]	Lin, CL	2003	217	Sub Arachnoid Haemorrhage	17 (8)	21 (10)	
Onset seizures independently predict poor outcome after subarachnoid hemorrhage[61]	Butzkueven, H	2000	412	Sub Arachnoid Haemorrhage	32 (8)	N/A	
Perioperative levetiracetam for prevention of seizures in supratentorial brain tumor surgery[19]	Zachenhofer, I	2011	78	Tumour	N/A	N/A	2 (2.5)
Add on phenytoin fails to prevent early seizures after surgery for supratentorial brain tumours[93]	de Santis, A	2002	200	Tumour	17 (8)	7 (3.5)	
Influence of Surgery and Antiepileptic Drugs on Seizures Symptomatic of Cerebral Tumours[194]	Franceschetti, S.	1990	128	Tumour	N/A	N/A	18 (14)
A prospective randomized trial of perioperative seizure prophylaxis in patients with intraparenchymal brain tumors[45]	Wu, AS	2013	123	Tumour	3 (2.4)	4 (3.2)	
Use of peri-operative anti-epileptic drugs in patients with newly diagnosed high grade malignant glioma: a single center experience[195]	Lwu, S	2010	164	Tumour	N/A	N/A	2 (1)
Risk Factors and Phenytoin Prophylaxis for Early Post-Traumatic Seizures among Patients with Traumatic Brain Injury[196]	Hup, CK	2010	157	Trauma	N/A	N/A	11 (7)
Increased incidence and impact of nonconvulsive and convulsive seizures[54]	Vespa PM	1999	94	Trauma	14 (67)	7 (33)	
A prospective multicentre comparison of Levetiracetam versus phenytoin for early post traumatic seizure prophylaxis[197]	Inaba K.	2011	813	Trauma	2 (17)	10 (83)	
Traumatic epilepsy after closed head injuries[174]	Jennett, B. and Lewin, W.	1960	750	Trauma	30 (66)	16 (34)	
Early seizures after mild closed head injury[198]	Lee, ST and Lui, TN.	1992	4332	Trauma	43 (43)	57 (57)	
A randomised double blind study of phenytoin for the prevention of post traumatic seizures[40]	Temkin, NR.	1990	404	Trauma	14 (40)	21 (60)	
Early seizures after moderate closed head injury[172]	Lee, ST.	1995	2574	Trauma	46 (43)	60 (57)	
Do prophylactic anticonvulsant drugs alter the pattern of seizures after craniotomy?[95]	Foy, PM	1992	276	Craniotomy	N/A	N/A	34 (12)
Post-Operative epilespy: A double-blind trial of phenytoin after craniotomy[88]	North, JB	1980	203	Craniotomy	N/A	N/A	12 (6)
Phenytoin and postoperative epilepsy A double-blind study[199]	North, JB	1983	281	Craniotomy	N/A	N/A	18 (6)
Levetiracetam compared to phenytoin for the prevention of postoperative seizures after	Kern, K	2012	235	Craniotomy	N/A	N/A	9 (4)

craniotomy for intracranial tumours in patients without epilepsy[15]								
Epilepsy after craniotomy and the place of prophylactic anticonvulsant drugs: discussion paper[200]	Shaw, MD. and Foy, PM.	1991	877	Craniotomy	N/A	N/A	19 (2)	
Efficacy and tolerability of levetiracetam versus phenytoin after supratentorial neurosurgery[201]	Milligan, TA	2008	315	Craniotomy	N/A	N/A	10 (3)	
Comparative double blind clinical trial of phenytoin and sodium valproate as anticonvulsant prophylaxis after craniotomy: efficacy, tolerability, and cognitive effects[94]	Beenen, LFM	1999	100	Craniotomy	4 (4)	2 (2)		
Incidence and Management of Late Postsurgical Seizures in Clinical Practice[202]	Bartolini, E	2012	100	Craniotomy	N/A	N/A	13 (13)	
Prophylactic anticonvulsants for prevention of immediate and early postcraniotomy seizures[203]	Horwitz NH	1989	185	Craniotomy	4 (44)	5 (56)		
Total Number of Subjects in all studies			24,457	Mean Percentage of Subjects Presenting with Seizures within (a)24 hours or (b)1- 7 days	(a) 61	(b) 38		
Number of Subjects Presenting with Seizures within (a)24 hours or (b)1- 7 days	(a) 512	(b) 283						

Studies were scrutinised for the number of patients presenting with seizures and the time to onset of seizures. When recorded, those seizures that presented within 24 hours, or within 7 days of the onset of brain injury were noted. The figures in bold indicate studies where early onset seizures were recorded up to 14 days. The values for the onset of seizures within 24 hours is > 50% in several studies where this value was recorded. This may have implications for the management of early onset seizures, particularly in traumatic brain injury where seizure prophylaxis may not be suitable

NA indicates data not available.

report a timeline for early-onset seizures, they present within 24 hours of the brain injury. Following severe traumatic brain injury, time to first seizure may be delayed beyond 7 days in subjects that require a craniectomy[90] (Table 5).

In qualifying the optimum duration of therapy, a consideration is given to the impact of early seizures on recovery and management, and the onset of the epileptogenic phenomena that leads to late-onset seizures.[204] Late-onset seizures are a consequence of an epileptogenic process promoted by the brain injury. However, currently available AEDs cannot modify this epileptogenic process and extension beyond 7 days to limit the epileptogenic process is not recommended.[204] The decision to stop the AED should be a clinical decision, considering the risk of seizures, and the impact of a seizure on clinical management. Alternative flexible paradigms to the 7-day model may have more practical application balancing these contradictory elements.

LEVETIRACETAM AND CONFLICT OF INTEREST

It has been argued that the drive to develop levetiracetam as neurosurgical seizure prophylaxis is compromised by pharmaceutical support for drug trials.[205,206] Levetiracetam is marketed as Keppra by UCB Pharma Ltd. and generic forms are marketed by several other manufacturers. Of the 32 clinical trials that considered the application of levetiracetam for seizure prophylaxis in neurosurgery, 11 described receiving support from UCB Pharma Ltd., either directly, through the free supply of the drug, travel grants, or other indirect support. It has been previously described that industry support for pharmaceutical trials is more likely to lead to a positive outcome that noncommercial trials.[205] This association between the support received for clinical trials of levetiracetam and positive outcome is observed in the clinical trials reviewed (Table 6).

SEIZURE PROPHYLAXIS: CLINICAL GUIDELINE FOR NEUROSURGERY

The decision to provide seizure prophylaxis is a balance of the adverse effects of antiepileptic therapy, the risk of developing seizures, and the perceived implications of a seizure on medical management with an arbitrary divide set at a seizure risk $>25\%$.[207]

A clinical guideline for seizure prophylaxis in neurosurgery is desirable, but conclusions derived from current research are equivocal and do not support the practice.[208] Equally, the medical management of patients with a single de novo unprovoked seizure, does not support the early introduction of AEDs.[207,209–211] Therefore, it is time to reevaluate the practice of seizure prophylaxis in neurosurgery.

The problem with seizure prophylaxis is that it may not be effective, seizures may present within 24 hours of a brain injury or after 7 days, and the effect of seizure prophylaxis may be detrimental to rehabilitation. The solution offered to this conundrum is to develop a flexible paradigm

TABLE 6. The Clinical Trials Where Levetiracetam Was Used For Seizure Prophylaxis Were Interrogated For Financial Support From Pharmaceutical Companies

Funding Origin	No. Trials (%)	Conclusion Supporting Levetiracetam	Conclusions Not Supporting Levetiracetam	Conclusions Supporting No Change
Pharmaceutical support	11 (34)	7	0	4
Nonpharmaceutical support	5 (16)	1	0	4
No conflict registered	16 (50)	1	1	14

The support was either direct trial funding or through funding of other trial costs such as travels. UCB was the only pharmaceutical company providing funding for these trials. The funded trials tended to support levetiracetam compared with those studies that did not report pharmaceutical funding.

for the management of seizures in neurosurgery, and to apply seizure prophylaxis only where seizures may compromise brain integrity through the detrimental effects of an elevation in intracranial pressure or a compromise of cerebral perfusion. Seizure prophylaxis may also be a pragmatic option, where consciousness is compromised through brain trauma or therapeutic coma, and clinical observation of seizure activity is difficult without cEEG monitoring. Once instigated, treatment would not be limited to 7 days; rather cessation of treatment would be dependent on an assessment of clinical need and a risk of subsequent seizures. A paradigm is suggested that accounts for the several opposing needs, but local factors may dictate an alternative paradigm (Fig. 1).

CONCLUSIONS

Clinical decisions are often made in the presence of some uncertainty.[212] Health care should be based on a combination of scientific evidence, clinical experience, economics, patient value judgments, and preferences. Seizures are not uncommon following brain injury, surgical trauma, hemorrhage, altered brain metabolism, hypoxia, or ischemic events. The impact of seizures in the immediate aftermath of injury may be a prolonged intensive care stay or compounding of the primary injury.

The aim of brain injury management is to limit the consequences of the secondary damage. The original intention of seizure prophylaxis was to limit the incidence of early-onset seizures. However, clinical trials have been

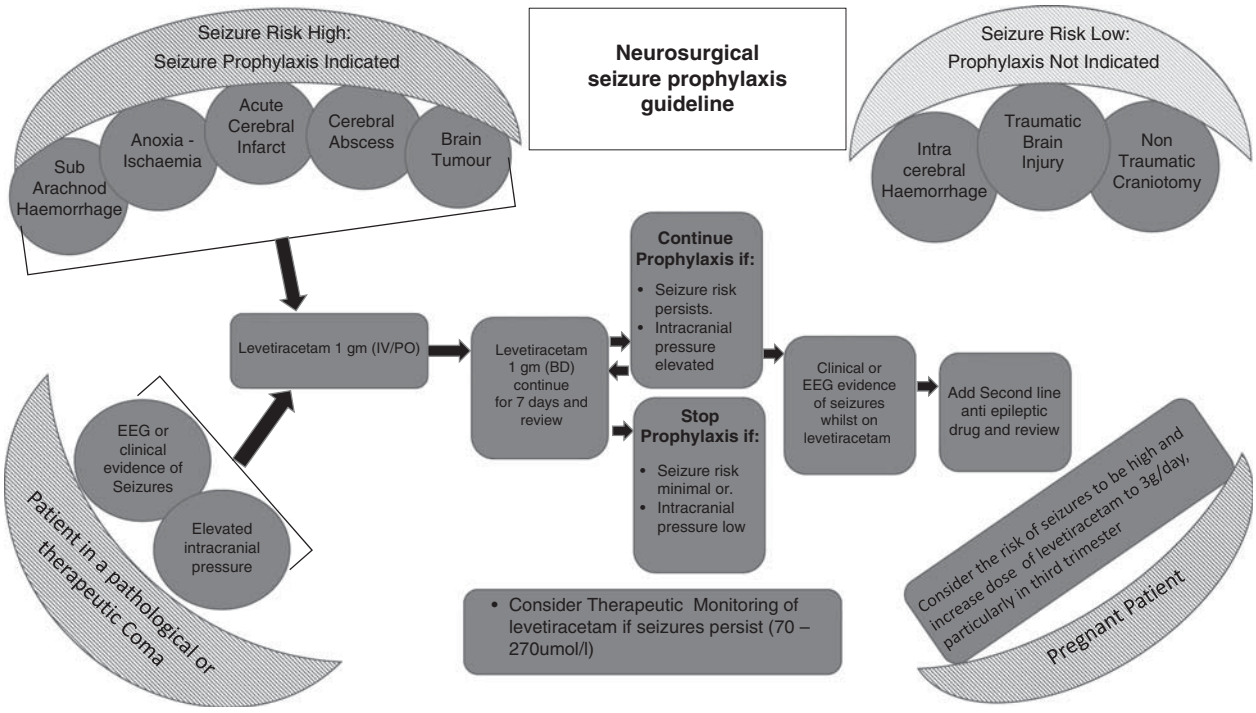


FIGURE 1. The indication for the use of seizure prophylaxis should consider the risk of seizures, the detrimental impact of a seizure on brain physiology, and the adverse effects of antiepileptic medication. Those conditions that are indicated for treatment are the result of an arbitrary risk of seizures being placed at >25%. Special consideration can be given to the unconscious patient, whether through the brain injury and a pharmacological coma. In those cases, seizures may not be apparent without 24-hour EEG monitoring. Prophylaxis should be considered, until the coma is reversed. Although seizures may present within 24 hours of the brain injury, the duration of treatment may not need to continue beyond 7 days unless clinical conditions dictate.

equivocal on this point, and there is concern about the adverse effects of phenytoin.

This review of the literature also raises concerns regarding the arbitrary division of seizures into early onset (7 d) and late onset (8 d and beyond). In many cases, seizures present within 24 hours or after 7 days of the injury, which is outside the current scope of seizure prophylaxis. There is no pathophysiological reason to divide trauma-related seizures into those timeframes. A solution to the conundrum is to reevaluate the practice of seizure prophylaxis. Prophylaxis could be offered to those where consciousness is compromised, seizures are masked, and the effect of a seizure will compromise the injured brain. Neurosurgical seizure management can consider which agent is most suitable, with most evidence in support of levetiracetam. Previous reviews have identified an increase cost associated with the use of levetiracetam, although current cost comparisons with phenytoin demonstrate a marginal price differential. Future clinical trials could reflect these considerations, and abandon the 7-d–only paradigm.

The aim of this review was to assimilate the literature with respect to seizure prophylaxis. The objective of the final guidance is not that is should be a directive, but a forum upon which further clinical research and audit could address the problems. The authors encourage a discussion of the merits of the paradigm suggested.

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