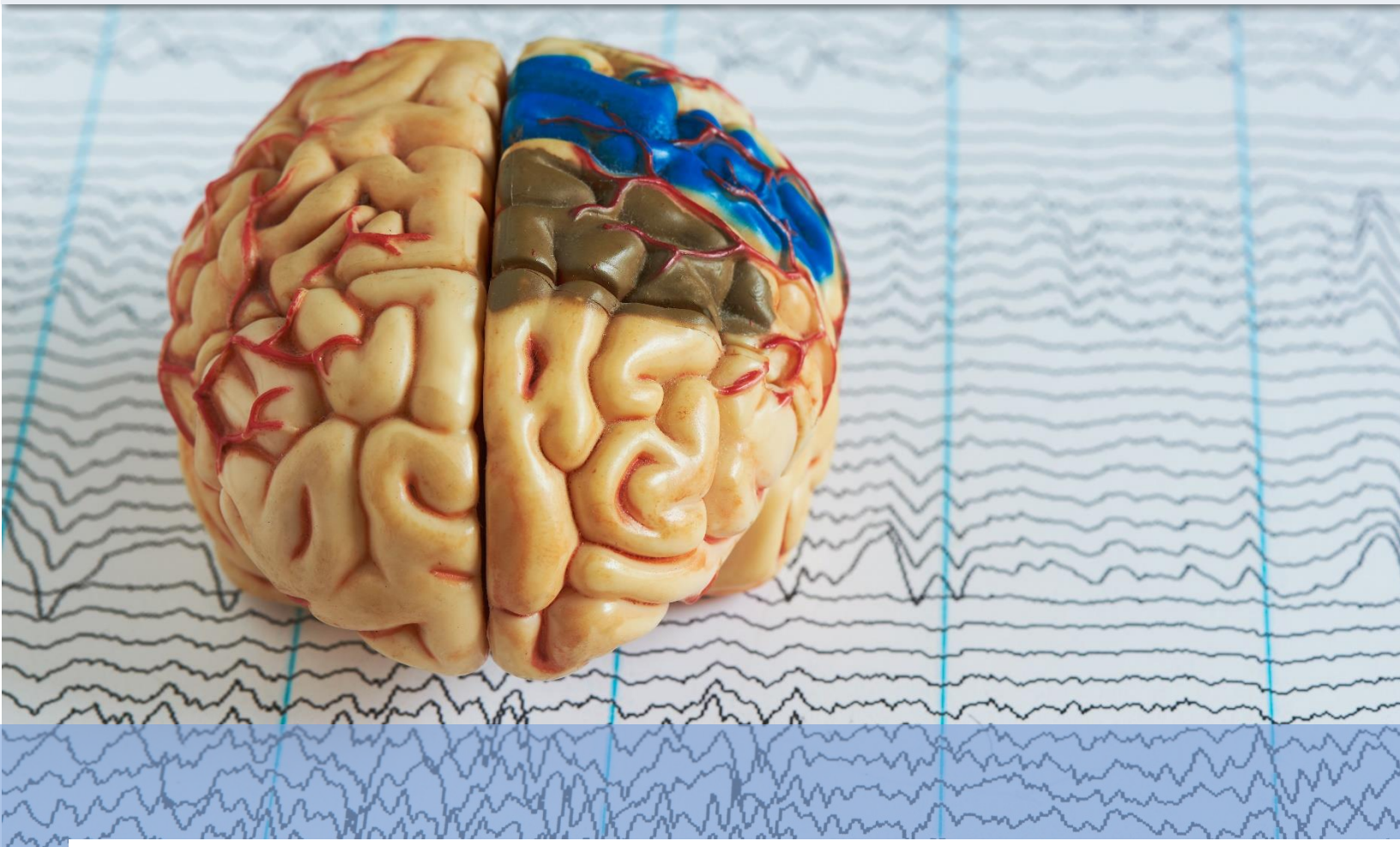
ERABI
EVIDENCE-BASED REVIEW
of moderate to severe
ACQUIRED BRAIN INJURY



POST-TRAUMATIC SEIZURE DISORDERS

FOLLOWING ACQUIRED BRAIN INJURY

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Disclaimer

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Conflict of Interest

In the context of ERABI development, the term “conflict of interest” (COI) refers to situations in which an author or ERABI staff member’s financial, professional, intellectual, personal, organizational or other relationships may compromise their ability to independently conduct this evidence-based review. No limiting conflicts were identified.

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Greetings from Dr. Robert Teasell,

Professor and Chair-Chief of Physical Medicine and Rehabilitation

The Collaboration of Rehabilitation Research Evidence (CORRE) team is delighted to present the Evidence-Based Review of moderate to severe Acquired Brain Injury (ERABI) *Fatigue and Sleep Disorders post Acquired Brain Injury.* Through collaboration of researchers, clinicians, administrators, and funding agencies, ERABI provides an up-to-date review of the current evidence in brain injury rehabilitation. ERABI synthesizes the research literature into a utilizable format, laying the foundation for effective knowledge transfer to improve healthcare programs and services.

We offer our heartfelt thanks to the many stakeholders who are able to make our vision a reality. Firstly, we would like to thank the Ontario Neurotrauma Foundation, which recognizes ERABI's capacity to lead in the field of brain injury evidence-based reviews and is committed to funding it. We would also like to thank the co-chairs of ERABI, Dr. Mark Bayley (University of Toronto) and Dr. Shawn Marshall (University of Ottawa) for their invaluable expertise and stewardship of this review. Special thanks to the authors for generously providing their time, knowledge and perspectives to deliver a rigorous and robust review that will guide research, education and practice for a variety of healthcare professionals. We couldn't have done it without you! Together, we are building a culture of evidence-based practice that benefits everyone.

We invite you to share this evidence-based review with your colleagues, patient advisors that are partnering within organizations, and with the government agencies with which you work. We have much to learn from one another. Together, we must ensure that patients with brain injuries receive the best possible care every time they require rehabilitative care – making them the real winners of this great effort!

Robert Teasell, MD FRCPC

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Preface

About the Authors

ERABI is internationally recognized and led by a team of clinicians and researchers with the goal of improving patient outcomes through research evidence. Each ERABI module is developed through the collaboration of many healthcare professionals and researchers.

Heather MacKenzie, MD, FRCPC is a consultant physiatrist in the spinal cord injury and brain injury rehabilitation programs at Parkwood Institute in London, Ontario, and an assistant professor in the Department of Physical Medicine & Rehabilitation at Western University. Her research focuses on the development of prognostic models and predicting outcomes after mild traumatic brain injury and concussion. Most recently, she completed a Master of Science degree in Epidemiology at the Harvard T. H. Chan School of Public Health.

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Amber Harnett, MSc, RN, CNF scholar, completed her MSc in pathology at Western University and the accelerated BScN program at Western University. Passionate about supporting and advocating for those with brain injuries, she also works as a research coordinator to improve the rehabilitation system through research synthesis, guideline development, knowledge translation, education and outreach, in the CORRE lab at Parkwood Institute.

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Dr. Shawn Marshall is a physician specializing in Physical Medicine and Rehabilitation (Physiatrist). He is the Division Head of Physical Medicine and Rehabilitation at the University of Ottawa and The Ottawa Hospital where he manages both in-patients and out-patient clinics for patients with concussion to severe traumatic brain injury. Dr. Marshall has a Master's degree in Clinical Epidemiology and is a Full Professor at the University of Ottawa in the Department of Medicine.

Dr. Cullen is the newly appointed Division Director for PM&R in the Department of Medicine and Chief of PM&R at HHSC and St Joseph's Healthcare. She has been the Chief of Staff and Chair of the Medical Advisory Committee at West Park Healthcare Centre for the last 10 years, actively seeking to promote system change and patient advocacy in an integrated system. Her goal is to enhance the quality of life of people with disabilities based on current best evidence.

Dr. Robert Teasell is Professor of Physical Medicine and Rehabilitation, Schulich School of Medicine and Dentistry, Western University and a Clinical Researcher at Lawson Research Institute in London, Ontario. He is a clinician at Parkwood Institute, St. Joseph's Health Care London.

Purpose

The Evidence-Based Review of Acquired Brain Injury (ERABI) is a systematic review of the rehabilitation literature of moderate to severe acquired brain injuries (ABI). It is an annually updated, freely accessible online resource that provides level of evidence statements regarding the strength of various rehabilitation interventions based on research studies. The ERABI is a collaboration of researchers in London, Toronto and Ottawa. Our mission is to improve outcomes and efficiencies of the rehabilitation system through research synthesis, as well as from providing the foundational research evidence for guideline development, knowledge translation, and education initiatives to maximize the real-world applications of rehabilitation research evidence.

Key Concepts

Acquired Brain Injury

For the purposes of this evidence-based review, we used the definition of ABI employed by the Toronto Acquired Brain Injury Network (2005). ABI is defined as damage to the brain that occurs after birth and is not related to congenital disorders, developmental disabilities, or processes that progressively damage the brain. ABI is an umbrella term that encompasses traumatic and non-traumatic etiologies.

TABLE 1 | Defining Acquired Brain Injury

Included in ABI definition	Excluded from ABI definition
Traumatic Causes • Motor vehicle accidents • Falls • Assaults • Gunshot wounds • Sport Injuries **Non-traumatic Causes** • Tumours (benign/meningioma only) • Anoxia • Subarachnoid hemorrhage (non-focal) • Meningitis • Encephalitis/encephalopathy (viral, bacterial, drug, hepatic) • Subdural Hematoma	**Vascular and Pathological Incidents** • Intracerebral hemorrhage (focal) • Cerebrovascular accident (i.e., stroke) • Vascular accidents • Malignant/metastatic tumours **Congenital and Developmental Problems** • Cerebral Palsy • Autism • Developmental delay • Down's syndrome • Spina bifida with hydrocephalus **Progressive Processes** • Alzheimer's disease • Pick's disease • Dementia • Amyotrophic Lateral Sclerosis • Multiple Sclerosis • Parkinson's disease • Huntington's disease

Given that 'ABI' can have multiple definitions, studies with an 'ABI' population can be equally heterogeneous in terms of the sample composition. Such studies may include any combination of

persons with TBI, diffuse cerebrovascular events (i.e., subarachnoid hemorrhage) or diffuse infectious disorders (i.e., encephalitis or meningitis). The vast majority of individuals with ABI have a traumatic etiology; therefore, much of the brain injury literature is specific to TBI. The terms ABI and TBI have been used intentionally throughout ERABI to provide more information about populations where relevant.

Moderate to Severe Brain Injury

ABI severity is usually classified according to the level of altered consciousness experienced by the patient following injury (Table 2). The use of level of consciousness as a measurement arose because the primary outcome to understand the severity of an injury is the Glasgow Coma Scale. Consciousness levels following ABI can range from transient disorientation to deep coma. Patients are classified as having a mild, moderate or severe ABI according to their level of consciousness at the time of initial assessment. Various measures of altered consciousness are used in practice to determine injury severity. Common measures include the Glasgow Coma Scale (GCS), the duration of loss of consciousness (LOC), and the duration of post-traumatic amnesia (PTA). Another factor used to distinguish moderate and severe brain injury is evidence of intracranial injury on conventional brain imaging techniques which distinguish severity of injury from a mild or concussion related brain injury.

TABLE 2 | Defining Severity of Traumatic Brain Injury, adapted from Veterans Affairs Taskforce (2008) and Campbell (2000)

Criteria	Mild	Moderate	Severe	Very Severe
Initial GCS	13-15	9-12	3-8	Not defined
Duration LOC	< 15minutes*	<6 hours	6-48 hours	>48 hours
Duration PTA	< 1hour*	1-24 hours	1-7 days	>7 days
	*This is the upper limit for mild traumatic brain injury; the lower limit is any alteration in mental status (dazed, confused, etc.).			

Methods

An extensive literature search using multiple databases (CINAHL, PubMed/MEDLINE, Scopus, EMBASE, and PsycINFO) was conducted for articles published in the English language between 1980–April 2022 that evaluate the effectiveness of any intervention/treatment related to ABI. The references from key review articles, meta-analyses, and systematic reviews were reviewed to ensure no articles had been overlooked. For certain modules that lacked research evidence the gray literature, as well as additional databases, were searched in order to ensure the topic was covered as comprehensively as possible.

Specific subject headings related to ABI were used as the search terms for each database. The search was broadened by using each specific database's subject headings, this allowed for all other terms in the database's subject heading hierarchy related to ABI to also be included. The consistent search terms used were "head injur*", "brain injur*", and "traumatic brain injur*". Additional keywords were used

specific to each module. A medical staff librarian was consulted to ensure the searches were as comprehensive as possible.

Every effort was made to identify all relevant articles that evaluated rehabilitation interventions/ treatments, with no restrictions as to the stage of recovery or the outcome assessed. For each module, the individual database searches were pooled, and all duplicate references were removed. Each article title/abstract was then reviewed; titles that appeared to involve ABI and a treatment/intervention were selected. The remaining articles were reviewed in full.

Studies meeting the following criteria were included: (1) published in the English language, (2) at least 50% of the study population included participants with ABI (as defined in Table 1) or the study independently reported on a subset of participants with ABI, (3) at least three participants, (4) ≥50% participants had a moderate to severe brain injury (as defined in Table 2), and (5) involved the evaluation of a treatment/intervention with a measurable outcome. Both prospective and retrospective studies were considered. Articles that did not meet our definition of ABI were excluded.

Interpretation of the Evidence

The levels of evidence (Table 3) used to summarize the findings are based on the levels of evidence developed by Sackett et al. (2000). The levels proposed by Sackett et al. (2000) have been modified; specifically, the original ten categories have been reduced to five levels. Level 1 evidence pertains to high quality randomized controlled trials (RCTs) (PEDro ≥6) and has been divided into two subcategories, level 1a and level 1b, based on whether there was one, or more than one, RCT supporting the evidence statement.

The evidence statements made in evidence-based reviews are based on the treatment of groups rather than individuals. There are times when the evidence will not apply to a specific case; however, the majority of patients should be managed according to the evidence. Ultimately, the healthcare professional providing care should determine whether an intervention is appropriate and the intensity with which it should be provided, based on their individual patient's needs. Furthermore, readers are asked to interpret the findings of studies with caution as evidence can be misinterpreted. The most common scenario occurs when results of a trial are generalized to a wider group than the evidence allows. Evidence is a tool, and as such, the interpretation and implementation of it must always be done with the known limitations in mind.

TABLE 3 | Levels of Evidence

Level	Research Design	Description
1A	Randomized Controlled Trial (RCT)	More than one RCT with PEDro score ≥6. Includes within subject comparisons, with randomized conditions and crossover designs
1B	RCT	One RCT with PEDro ≥6

2	RCT	One RCT with PEDro <6
	Prospective Controlled Trial (PCT)	Prospective controlled trial (not randomized)
	Cohort	Prospective longitudinal study using at least two similar groups with one exposed to a particular condition
3	Case Control	A retrospective study comparing conditions including historical controls
4	Pre-Post Trial	A prospective trial with a baseline measure, intervention, and a post-test using a single group of subjects
	Post-test	A prospective intervention study using a post intervention measure only (no pre-test or baseline measurement) with one or more groups
	Case Series	A retrospective study usually collecting variables from a chart review
5	Observational study	Using cross sectional analysis to interpret relations
	Clinical Consensus	Expert opinion without explicit critical appraisal, or based on physiology, biomechanics or “first principles”
	Case Reports	Pre-post or case series involving one subject

Strength of the Evidence

The methodological quality of each randomized controlled trial (RCT) was assessed using the Physiotherapy Evidence Database (PEDro) rating scale developed by the Centre for Evidence-Based Physiotherapy in Australia (Moseley et al., 2002). The PEDro is an 11-item scale; a point is awarded for ten satisfied criterion yielding a score out of ten. The first criterion relates to external validity, with the remaining ten items relating to the internal validity of the clinical trial. The first criterion, eligibility criteria, is not included in the final score. A higher score is representative of a study with higher methodological quality.

POST TRAUMATIC SEIZURE DISORDERS

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Summary of the Evidence

Intervention	Key Point Level of Evidence
PROPHYLAXIS OF POST-TRAUMATIC SEIZURES	
Pharmacological Interventions	
Anticonvulsants	
Phenytoin	Phenytoin, when compared to placebo, may be effective for the prophylaxis of early post-traumatic seizures; however, it may not prevent onset of late seizures in individuals with TBI. - *There is level 1b evidence that early administration of phenytoin may be effective in reducing the rate of early post-traumatic seizures in individuals with TBI (Temkin et al., 1990; Gul et al., 2019; Wohns et al., 1979; Young et al., 1979).* - *There is level 1b evidence (McQueen et al., 1983; Temkin et al., 1990; Young et al., 1983) that phenytoin may not be more effective than placebo in preventing late seizures post TBI.* - *There is level 3 evidence (Bhullar et al., 2014) that phenytoin may negatively impact recovery when compared to a placebo in patients with TBI.* - *There is level 4 evidence (Sabo et al., 1995) that prophylaxis using phenytoin may decrease occurrence of seizures in individuals treated surgically for chronic subdural hematoma.* The administration of fosphenytoin or carbamazepine with continuous EEG monitoring may be effective for the prevention of early post-traumatic seizures. - *There is level 2 evidence (Arai et al., 2018) that administration of fosphenytoin or carbamazepine, with continuous EEG monitoring, may be effective for the prophylaxis of early post-traumatic seizures in individuals with TBI.*
Levetiracetam	Extended treatment with levetiracetam may be effective for the reduction of in-hospital seizures in individuals with ABI. Levetiracetam may be as effective as phenytoin in the prevention of early post-traumatic seizures. - *There is level 1b evidence (Human et al., 2018) that levetiracetam may reduce the occurrence of in-hospital seizures in individuals with ABI.* - *There is level 1b evidence (Szaflarski et al., 2010; Steinbaugh et al., 2012), level 2 evidence (Inaba et al., 2013; Gabriel & Rowe, 2014; Javed et al., 2016; Jones et al., 2008; Kruer et al., 2013; Khan et al., 2016; Patanwala et al., 2016) and level 3 evidence (Radic et al., 2014) that there is no significant difference in the rate of early post-traumatic seizures when comparing phenytoin to levetiracetam in patients with ABI.* - *There is level 2 evidence (Gabriel & Rowe, 2014) that phenytoin is not more effective in reducing the rate of late post traumatic seizures compared to levetiracetam in patients with ABI.*

	- *There is level 1b evidence (Younus et al., 2018) that levetiracetam is more effective than phenytoin for the reduction of seizures at 7-10 days post-injury in patients with moderate to severe TBI.* - *There is level 3 evidence (Radic et al., 2014) that levetiracetam may be associated with a higher risk for electrographic seizures compared to phenytoin among patients with midline shift.*
Carbamazepine	The administration of fosphenytoin or carbamazepine with continuous EEG monitoring may be effective for the prevention of early post-traumatic seizures. - *There is level 2 evidence (Arai et al., 2018) that administration of fosphenytoin or carbamazepine, with continuous EEG monitoring, may be effective for the prophylaxis of early post-traumatic seizures in individuals with TBI.*
Lacosamide	Lacosamide may be as effective as phenytoin for post-traumatic seizure prophylaxis, with more tolerable side effects; however, more research is needed. - *There is level 2 evidence (Kwon et al, 2019) that lacosamide may be as effective as phenytoin for the prophylaxis of post-traumatic seizures; however, lacosamide may have more tolerable side effects.*
Valproic Acid	Valproic acid may not be effective in for the prevention of post-traumatic seizures when compared to no treatment for the first seven days post injury. Valproic acid and phenytoin may have similar effectiveness regarding rates of early seizures, late seizures, or mortality. - *There is level 1b evidence (Temkin et al., 1999; Dikmen et al., 2000) that the valproic acid and phenytoin may have similar efficacy for the prophylaxis of both early and late seizures following TBI.* - *There is level 2 evidence (Ma et al., 2010) that valproic acid may not be effective for the prevention of early post-traumatic seizures.*
Barbiturates	
Phenobarbital	Phenobarbital alone may not be effective in preventing late post-traumatic seizures. Phenobarbital combined with phenytoin may reduce the occurrence of late post-traumatic seizures. - *There is level 2 evidence (Manaka et al., 1992) that prophylaxis with phenobarbital alone may not reduce the occurrence of late post-traumatic seizures among individuals with TBI.* - *There is level 2 evidence (Servit & Musil, 1981) that prophylaxis with phenobarbital in combination with phenytoin may reduce the occurrence of late post traumatic seizures.* - *There is level 4 evidence (Murri et al., 1992) that therapy with phenobarbital during the first 12 months post injury may have a prophylactic effect on PTE.*

Multiple Medications	Phenytoin Phenytoin and levetiracetam may have similar effectiveness and may have more effectiveness that valproate for the prophylaxis of early and late post-traumatic seizures. - *There is level 2 evidence (Kancharla et al., 2019) that phenytoin and levetiracetam may have similar effectiveness for the prophylaxis of early and late post-traumatic seizures and may both be more effective than valproate.* Topiramate, gabapentin, levetiracetam may help achieve a faster remission of PTE, when compared to phenytoin, phenobarbital, carbamazepine. - *There is level 2 evidence (Šapina and Ratković, 2017) that new generation anticonvulsants (topiramate, gabapentin, and levetiracetam) may result in faster remission of post-traumatic seizures, when compared to standard anticonvulsants (phenytoin, phenobarbital, and carbamazepine).* Carbamazepine, phenobarbital and carbamazepine, phenobarbital, phenytoin, or clonazepam may not be effective for late seizure prophylaxis post severe TBI. - *There is level 2 evidence (Formisano et al., 2007) that carbamazepine, phenobarbital and carbamazepine, phenobarbital, phenytoin, or clonazepam may not be effective for the prophylaxis of PTE in individuals with severe TBI.* The use of antiseizure medication may result in a significant lower risk of developing early PTS; however, findings from studies that did not compared medications should be interpreted with caution. - *There is level 2 evidence (Kale et al., 2018) that prophylactic anticonvulsants may not be continued beyond the first postoperative week; however, findings from this study should be interpreted with caution.* - *There is level 4 evidence (Pingue et al., 2021) that use of anticonvulsant medication may be effective for the prevention of early post traumatic seizures. However, further research comparing medications is needed.*
Non-Pharmacological Interventions	
Auricular Electroacupuncture	Auricular electroacupuncture may be effective for the prophylaxis of post-traumatic seizures following severe TBI. However, more research is needed. - *There is level 2 evidence (Shen & Jiang, 2019) that auricular electroacupuncture may reduce the incidence of late post-traumatic epilepsy in individuals with severe TBI.*
MANAGEMENT OF POST-TRAUMATIC SEIZURES	
Pharmacological Interventions	
Carbamazepine	Replacing phenytoin and phenobarbital with carbamazepine may help reduce seizure frequency in individuals with PTS. - *There is level 4 evidence (Wroblewski et al., 1989) that switching from phenytoin or phenobarbital to carbamazepine may be associated with a reduced seizure frequency among individuals with previous post traumatic seizures.*

Topiramate	Topiramate may be well tolerated and effective in reducing seizures post ABI; however, more research is needed to determine its effectiveness for injuries of traumatic etiology. - *There is level 4 evidence (Liu et al., 2009) that topiramate may be effective in reducing seizures in individuals with ABI.*
Midazolam	An intramuscular injection of midazolam may help to stop seizures in individuals with brain injuries. - *There is level 4 evidence (Wroblewski et al., 1992b) that an intramuscular injection of midazolam may be effective in aborting active seizure activity.*
Surgical Interventions	
Surgical Resection	Surgical resection may be effective in reducing seizures in certain subpopulations of individuals with brain injuries, particularly among individuals in whom the seizure focus can be accurately localized. - *There is level 2 evidence (Hitti et al., 2020) that post-traumatic epilepsy attributable to mesial temporal sclerosis treated with temporal lobectomy may be associated with favourable clinical outcomes in the majority of individuals.* - *There is level 4 evidence (Marks et al., 1995) that individuals in whom the seizure focus can be accurately localized may benefit from surgical resection for post-traumatic seizures.* - *There is level 4 evidence (Hakimian et al., 2012) that extratemporal resection with or without temporal lobectomy may be effective for controlling medically intractable post-traumatic epilepsy.*
Responsive Neurostimulation and Vagal Nerve Stimulation	More research is needed to determine the role of vagal nerve stimulation and responsive neurostimulation in the treatment of post-traumatic epilepsy. - *There is level 2 evidence (Hitti et al., 2020) that vagal nerve stimulation and responsive neurostimulation may be effective in reducing seizure frequency in certain individuals with PTE; however, more research is needed.*
RISK OF POST-TRAUMATIC SEIZURES	
Pharmacological Interventions	
Corticosteroids	
Dexamethasone	Dexamethasone may increase the risk of late seizures when administered within one day post TBI. - *There is level 2 evidence (Watson et al., 2004) that glucocorticoid administration within 1 day post injury may put persons with severe TBI at a higher risk of late seizure development*

Stimulants	
Methylphenidate	Methylphenidate does not appear to increase seizure frequency among individuals with late PTS. - *There is level 4 evidence (Wroblewski et al., 1992a) that methylphenidate does not increase the risk of seizures among individuals with late PTS.*
Surgical Interventions	
Craniotomy and Craniectomy	The incidence of seizures may not be different following craniectomy when compared to craniotomy. Acute post-craniectomy seizures occur in 10.8% of patients, mostly within 3 days of the procedure. - *There is level 2 evidence (Won et al., 2017; Ramakrishnan et al., 2015) that there may be no difference in seizure occurrence among individuals who underwent craniectomy when compared to those who underwent craniotomy post TBI.* - *There is level 4 evidence (Huang et al., 2015) that acute post-craniectomy seizures may occur in 10.8% of patients, with most taking place within three days of the surgery.*

Introduction

Post-traumatic seizures (PTS) are a serious consequence of moderate to severe brain injury, and are particularly prevalent in individuals with traumatic injuries presenting with hemorrhage (Fordington & Manford, 2020). Post-traumatic seizure disorders have been defined in the *Practice Parameter of the Antiepileptic Drug Treatment of Post-traumatic Seizures* by the Brain Injury Special Interest Group of the American Academy of Physical Medicine and Rehabilitation (1998) (Table 4). This module is intended to provide insight into the frequency and clinical presentation of PTS, as well as any evidence-based interventions that address the prophylaxis and management of PTS in individuals with moderate to severe brain injuries.

TABLE 4 | Definitions of Post-Traumatic Seizures (p.595; (Brain Injury Special Interest Group, 1998))

Term	Definition
Seizure	Discrete clinical event that reflects a temporary physiologic dysfunction of the brain characterized by excessive and hypersynchronous discharge of cortical neurons.
Post-Traumatic Seizure	An initial or recurrent seizure episode not attributable to another obvious cause after penetrating or non-penetrating TBI. The term encompasses both single and recurrent events.
Immediate Post-Traumatic Seizure	A seizure due to TBI occurring within the first 24 hours of injury.
Early Post-Traumatic Seizure	A seizure due to TBI occurring within the first week of injury.

Late Post-Traumatic Seizure	A seizure due to TBI occurring after the first week of injury.
Post-Traumatic Epilepsy	A disorder characterized by recurrent late seizure episodes not attributable to another obvious cause in patients following TBI. The term should be reserved for *recurrent*, late post-traumatic seizures.
Nonepileptic Seizures	Episodic behavioural events that superficially resemble epileptic attacks but are not associated with paroxysmal activity within the brain.
Antiepileptic Drug Prophylaxis	In the context of post-traumatic seizures, antiepileptic drug treatment administered to prevent seizures in patients who are at risk but have not yet manifested seizures.
Epilepsy	A condition characterized by recurrent unprovoked seizures.
Status Epilepticus	More than 5 minutes of continuous seizure activity or two or more sequential seizures without full recovery of consciousness between seizures.

Incidence of Post-Traumatic Seizures

Post-traumatic epilepsy (PTE) is a life-long complication of TBI and involves recurrent unprovoked seizures occurring at least one week post injury (Verellen & Cavazos, 2010). It is believed that up to 20% of structural epilepsy in the general population is a result of TBI (Bushnik et al., 2012). In young adults TBI is the leading cause of epilepsy (Annegers, 1996).

Of all patients with TBI who are hospitalized, 5% to 7% will experience PTS. However, the incidence of PTS is much higher on rehabilitation units (as high as 18%), which reflects increased injury severity and the presence of a higher number of risk factors in this population (Armstrong et al., 1990; Bontke et al., 1993; Cohen & Groswasser, 1991; Kalisky et al., 1985; Sazbon & Groswasser, 1990; Sundararajan et al., 2015; Wang et al., 2013a). The incidence of late post-traumatic seizures (LPTS) ranges from 5% to 19% (Bushnik et al., 2012; Zhao et al., 2012). According to Pingue et al. (2021), during an observation period from acute care to inpatient rehabilitation, it was reported that 19.4% of individuals presented with seizure activity.

Post-traumatic epilepsy usually develops within the first year following injury, and the risk remains high within two years post injury (Di Luca & de Lacerda, 2013; Lamar et al., 2014; Lucke-Wold et al., 2015).In a study by Ritter et al., 2016, the highest incidence (8.9%) of post-traumatic seizures (PTS) occurred during hospitalization within the initial 24 hours post-injury (Ritter et al., 2016). Zhao et al. (2012) found that when seizures occurred post-injury, 88.7% of patients were diagnosed as late seizures; with the majority of those (66%) occurring between 10 days and three years post-injury.

For those who sustain a severe non-penetrating TBI, approximately 11% will experience LPTS and for those who have a TBI as the result of a penetrating injury, the incidence increases to 13-50% (Ascroft, 1941; Caveness & Liss, 1961; Malav et al., 2015; Yablon, 1993). Severity of TBI and risk of seizures are strongly related, particularly for those with penetrating injuries (Annegers et al., 1998); individuals

presenting with lower GCS scores have been found to be more likely to develop seizures (Malav et al., 2015).

A study examining 236,164 individuals with TBI found that 2.4% had pre-existing epilepsy or a seizure disorder (Wilson & Selassie, 2014); persons with pre-existing epilepsy or seizure disorder may also aggravate the severity of TBI and increase the risk of were more likely to have sustained a severe TBI and have had repetitive TBI (Wilson & Selassie, 2014).

Risk Factors for Post-Traumatic Seizures and Epilepsy

Risk Factors for Late Post-Traumatic Seizures (p.310; (Yablon & Dostrow, 2001))

- Age (adults > children)
- Alcohol use
- Family history
- Bone/metal fragments
- Depressed skull fracture
- Focal contusions/injury
- Focal neurologic deficits
- Lesion location
- Dural penetration
- Intracranial hemorrhage
- Injury severity
- Early post-traumatic seizures

There are several patient and injury characteristics that increase the likelihood of developing PTS. These include increased injury severity (Glasgow Coma Scale (GCS) score of less than 10, prolonged length of coma, prolonged length of post-traumatic amnesia), depressed skull fractures, cortical contusions, subdural hematomas, epidural hematomas, intracerebral hematomas, penetrating injuries and wounds with dural penetration, a seizure within the first week of injury, being male, older age, and having had multiple neurosurgical procedures (Brain Injury Special Interest Group, 1998; Dikmen et al., 1991; Englander et al., 2003; Krause-Titz et al., 2016; Walker et al., 2015; Wang et al., 2013b; Yablon, 1993; Zhao et al., 2012). Relative risk for developing PTS is strongly related to the head injury severity; while the relative risk for developing PTS is 1.5 times greater in individuals with mild TBI compared to the general population, it is 4 times and 29 times greater for those with moderate and severe TBI respectively (Herman, 2002).

Older age has also been reported as a risk factor for PTE, with highest incidence reported in individuals 30 to 54 years old, and in individuals over 60 years old (Ferguson et al., 2010; Zhao et al., 2012). Furthermore, individuals with 3 or more comorbid conditions, and/or depression before or at the time of their TBI are more likely to develop PTE (Ferguson et al., 2010). According to a meta-analysis conducted by Xu et al. (2017), risk factors for PTE include: being male, previous alcohol abuse, loss of consciousness at time of TBI, post-traumatic amnesia, and focal neurological signs.

Diamond et al. (2014) examined genetic variance and PTE development in 256 individuals with moderate to severe TBI. The authors found that higher cerebrospinal fluid and serum IL-1β (a potential biomarker for epilepsy) ratios were associated with an increased risk of PTE (Diamond et al., 2014). However, given

that this study is one of the first studies to explore genetic variability, more studies are needed before firm conclusions can be made.

It is important to identify patients who are at high-risk of developing PTS as these patients may benefit from pharmacological seizure prophylaxis. According to Yablon and Dostrow (2001), the clinical characteristics of the patient, the injury, and information obtained from neuroimaging and electrophysiologic assessment techniques can be used to identify those at high risk for developing seizure disorders post-injury.

Onset

The risk of epilepsy is highest within the first two years following brain trauma (Dikmen et al., 1991; Englander et al., 2003; Yablon, 1993), with 90% of individuals experiencing their first seizure by the end of the second year (Agrawal et al., 2006). Zhao et al. (2012) reported that among patients with PTE, 66% developed seizures within the first 6 months, 9.9% between 7 and 12 months, 11.7% between 13 and 24 months, and 8.5% between 25 and 36 months; additionally, the authors reported that the incidence of seizures beginning later than three years post injury was 5%. Further, Wang et al. (2013b) found that 9.8% of individuals with TBI experienced PTS within the first 2 years, with occurrence rates at 6 months and 1 year at 59.9% and 78.1%, respectively.

Although the risk of developing PTS is highest early after the injury (Temkin, 2001), the risk remains high for a period of years. As brain injury severity increases, the period of time for which a survivor is at risk of developing PTS also increases. After 5 years, adults with mild TBI no longer have a significantly increased risk relative to the general population (Annegers et al., 1998), whereas those with moderate or severe TBI, or penetrating TBI remain at increased risk for more than five years post-injury (Annegers et al., 1998; da Silva et al., 1992; Pagni, 1990; Salazar et al., 1985). Moreover, military personnel suffering severe penetrating missile brain injuries show an elevated risk for more than 15 years after the injury (Annegers et al., 1998; Caveness et al., 1979; Feeney & Walker, 1979; Salazar et al., 1985; Weiss et al., 1983). Those with penetrating trauma typically have their first unprovoked seizure sooner than those patients with non-penetrating trauma (Kazemi et al., 2012).

In a study by Di Luca and Lacerda (2013), unprovoked seizures occurred at a median time of one year post-injury; this was influenced by injury severity, as well as age at the time of injury, with patients older than 24 years of age developing seizures faster than younger patients. However, in another study, the authors reported that young people were more likely to experience PTS after injury (Wang et al., 2013b). In addition, individuals who have undergone surgical evacuation procedures may present with an increased risk of immediate/early PTS (Ritter et al., 2016).

Recurrence

Seizure recurrence is an important factor in the determination of disability, likelihood of employment, and quality of life, and has been associated with increased health care costs (Baker et al., 1997; Yablon & Dostrow, 2001). After a brain insult, there is a latency period where epileptogenesis can occur; increases in excitability due to molecular and cellular alterations may progress into unprovoked recurrent seizures (Lamar et al., 2014; Lucke-Wold et al., 2015).

Early seizures are likely due to the brain insult and the recurrence rate for seizures that occur in this time period is low (Lamar et al., 2014). Earlier studies have reported that approximately one-half of patients with EPTS experience only a single seizure with no recurrence, while another quarter experience a total of two to three seizures (De Santis et al., 1979; Kollevold, 1979). More recent evidence suggests that, among patients who experience EPTS, 20-30% will experience LPTS (Yablon & Dostrow, 2001). The risk of seizure recurrence for LPTS occuring greater than one week post-injury is higher compared to that for early PTS and may be more representative of epilepsy (Lamar et al., 2014).

In a study conducted by Zhao et al. (2012), 5.7% of patients with TBI experienced seizures more than once a week, 69.5% more than once a month, and 24.8% had a seizure frequency greater than once a year. The following table provides a summary of the onset, recurrence and clinical presentation of post-traumatic seizures (Yablon & Dostrow, 2001).

TABLE 5 | Summary of Onset, Recurrence, and Clinical Presentation of Post-Traumatic Seizures

Feature	Reference
20 – 30 % of patients with early PTS experience a late seizure.	(Yablon & Dostrow, 2001)
Seizure onset after the first week is associated with a much higher likelihood of seizure recurrence.	(Haltiner et al., 1997; Walker & Yablon, 1961)
Seizure frequency within the first-year post-injury may predict future seizure recurrence.	(Salazar et al., 1985)
Persistent PTS may be seen more commonly with partial seizures and less commonly with generalized seizures.	(Salazar et al., 1985)
A small number of patients experience frequent seizure recurrences, apparently refractory to conventional anti-seizure therapy.	(Haltiner et al., 1997; Pohlmann-Eden & Bruckmeir, 1997)

Clinical Presentation of Post-Traumatic Seizures

In patients who present with post-traumatic epilepsy, seizures are either generalized or focal, although both types can coexist (Agrawal et al., 2006). In a case series, Wiedemayer et al. (2002) reported that the first epileptic seizure was generalized in 69 patients (63.3%) and partial in 40 patients (36.7%); with 58 patients (53.2%) experiencing a second early seizure during the follow-up period. Similarly, in a study examining 66 individuals who developed LPTS, it was determined that 79% had generalized seizures and 21% had focal seizures (Englander et al., 2003). In addition, there has also been a correlation found between the type and frequency of seizures; individuals with simple or complex partial seizures may experience a higher frequency of seizures (Kazemi et al., 2012).

Based on multiple studies, the incidence by seizure type has been reported as follows: complex or simple partial seizures with secondary generalization, 16%-77% (Di Luca & de Lacerda, 2013; Kazemi et al., 2012; Sapina et al., 2014; Zhao et al., 2012); generalized tonic-clonic seizures, 30%-53.6% (Di Luca & de Lacerda, 2013; Zhao et al., 2012; Zheng et al., 2013); simple partial seizures, 14%-42.3% (Zhao et al., 2012; Zheng et al., 2013); complex partial seizures, 4.1%-16% (Sapina et al., 2014; Zhao et al., 2012; Zheng et al., 2013); and generalized atonic seizures, 2% (Di Luca & de Lacerda, 2013). In another study, it was reported that focal epilepsy was the most common subtype of PTE, diagnosed in 93% of patients and arising most commonly from the temporal and frontal lobes; more specifically, 57% of patients had temporal lobe epilepsy, 35% had frontal lobe epilepsy, 3% had parietal lobe epilepsy, and another 3% had occipital lobe epilepsy (Gupta et al., 2014).

Influence on Neurological Recovery and Functional Status

Neurological recovery can be influenced by PTS (Hernandez & Naritoku, 1997; Yablon & Dostrow, 2001). Yablon and Dostrow (2001) have noted that, in rodent models, brief and infrequent PTS occurring early after brain injury do not appear to impact functional recovery; however, more severe and widespread seizures occurring within the first 6 days post-injury can result in permanent impairments of functional recovery.

Post-traumatic seizures (PTS) may lead to cognitive and behavioural disorders (Yablon & Dostrow, 2001). Patients with PTS can experience persistent behavioural abnormalities and a higher incidence of psychiatric-related hospitalizations even compared to patients with penetrating TBI who do not experience PTS (Swanson et al., 1995). Some comorbidities of PTE may include sensorimotor difficulties (e.g., vision disturbances), cognitive impairment (e.g., mental fatigue, difficulties with memory), psychiatric disorders (e.g., depression, PTSD), and sleep disorders (e.g., insomnia, sleep apnea) (Golub & Reddy, 2022).

Post-traumatic seizures can have a significant impact on quality of life, affecting recreation, job opportunities and independence (Piccenna et al., 2017). Recurrent PTS may exert a negative impact on functional status following TBI, an adverse effect independent of the severity of the injury (Barlow et al., 2000; Schwab et al., 1993). In the case of penetrating TBI, PTS have been reported to be an important and independent factor which affects both employment status and cognitive performance (Schwab et al., 1993). However, in the case of non-penetrating TBI, the impact of PTS on functional prognosis and cognition is less clear (Armstrong et al., 1990; Asikainen et al., 1999). Within a population of individuals with LPTS, Kolakowsky-Hayner and colleagues (2013) discovered that occupational and social integration were the most difficult areas for recovery post-injury. However, Haltiner et al. (1997) found no significant differences at 1 year as a consequence of LPTS in terms of neuropsychological performance and psychosocial functioning when adjusted for injury severity. Asikainen et al. (1999) found that patients with PTS did have poorer outcomes on the Glasgow Outcome Scale. A more recent study found that of individuals with LPTS, 20% were severely disabled, 52% moderately disabled, and 28% had a good recovery, as measured by the Glasgow Outcome Scale Extended. No significant differences in

employment outcome associated with the presence of PTS have been found (Asikainen et al. (1999). Further, Kolakowsky-Hayner et al. (2013) found that among a group of individuals with TBI-LPTS, 40% (7 of 20) of individuals who were driving prior to injury had their license suspended due to their first seizure, and 3 were able to re-obtain their license.

Status Epilepticus

Status epilepticus can be defined as either more than 5 minutes of continuous seizure activity or two or more sequential seizures without full recovery of consciousness between seizures (Betjemann & Lowenstein, 2015). The spectrum of status epilepticus severity depends on the type of seizure and the type of underlying pathology, as well as patient comorbidities and timing of clinical management (Pichler & Hocker, 2017). In terms of onset and presentation, seizures can be focal or generalized, and either convulsive or non-convulsive; additionally, patients may present with preserved, altered or lost consciousness (Seinfeld et al., 2016). Status epilepticus is regarded as the most serious of the complications of PTS. In individuals with traumatic brain injury, status epilepticus is associated with increased mortality and poor outcomes such as longer hospitalizations and a higher risk of discharge to a skilled nursing facility (Dhakar et al., 2015). Fortunately, clinically apparent status epilepticus and simple partial status epilepticus are infrequent complications of PTS (Kollevold, 1979), with only 0.16% of individuals hospitalized with TBI with status epilepticus (Dhakar et al., 2015).

Mortality

Individuals who present with LPTS following TBI have nearly three times the mortality rate of those with without LPTS; further, those who died in the LPTS group did so at a younger age (Englander et al., 2009). In addition, mortality has also been reported to be high in individuals with status epilepticus of traumatic etiology (Betjemann & Lowenstein, 2015). Yablon and Dostrow (2001) have noted that the complications of a single LPTS are no different than those seen after any seizure and are generally minimal. However, increased seizure frequency and severity are associated with an increased risk of mortality and morbidity.

PROPHYLAXIS OF POST-TRAUMATIC SEIZURES

Pharmacological Interventions

Anticonvulsants

Schierhout and Roberts (2001) reported that a seizure occurring soon after head injury may cause secondary brain damage by increasing the metabolic demands of the brain, increasing intracranial

pressure, and leading to excessive amounts of neurotransmitter release. For this reason, the primary therapeutic objective in the use of anticonvulsant drugs has been the prevention of early seizures in an attempt to minimize the extent of secondary brain damage following TBI. Phenytoin is the most extensively studied agent, while more limited research has been conducted on other anticonvulsants such as valproate, carbamazepine and levetiracetam (Wat et al., 2019).

Some anticonvulsant drugs have been shown to have neuroprotective properties in animal studies. For example, following hypoxia, phenytoin has been linked with reduced neuronal damage in neonatal rats (Vartanian et al., 1996) and in rat hippocampal cell cultures (Tasker et al., 1992). Experimental evidence suggests that the neuroprotective effects of phenytoin are related to a blockage of voltage dependent sodium channels during hypoxia (Tasker et al., 1992; Vartanian et al., 1996) which would be expected to decrease the spread of calcium-induced neurotoxicity following hypoxic brain injury. As noted by Schierhout and Roberts (2001), this suggests that anti-epileptics may have beneficial properties which may be independent of their proposed anti-seizure activity.

Conversely, anti-epileptic drugs have been shown to have toxic effects in stable patients, with impaired mental and motor function being the most common adverse effects; serious adverse effects, including deaths as a result of hematological reactions, have been also reported (Reynolds et al., 1998). Schierhout and Roberts (2001) have suggested that the injured brain's response to anticonvulsants may be such that toxic effects could be more pronounced and neurological recovery may be delayed.

Studies have largely shown favourable results for the efficacy of anti-epileptic drug prophylaxis for EPTS; however, studies investigating chronic prophylaxis for LPTS have been less impressive. This section summarizes the literature to date, which has explored the use of various drugs for seizure prevention.

Phenytoin

Phenytoin is an anticonvulsant used for the treatment of tonic-clonic, partial seizures and status epilepticus (Patocka et al., 2020). Phenytoin has been widely used in practice for the prophylaxis of EPTS occurring within the first week post injury (Vella et al., 2017).

TABLE 6 | Phenytoin for the Prophylaxis of Post-Traumatic Seizures

Author, Year Country Study Design Sample Size	Methods	Outcome
Dikmen et al. (1991) USA RCT PEDro=6 $N_{Initial}$=244, N_{Final}=124	**Population:** TBI; *Phenytoin Group (n=104)*: Mean Age=30.9yr; Gender: Male=82, Female=22; Median GCS=11. *Placebo Group (n=101):* Mean Age=32.9yr; Gender: Male=70, Female=31; Median GCS=9. **Treatment:** Patients were randomized to receive phenytoin or a placebo for 1yr post-injury. Patients were then observed for another 1yr while unmedicated.	1. From 1 to 12mo, more participants in the treatment group stopped receiving their assigned drug ($p<0.01$) due to idiosyncratic reactions and requests. 2. Those severely injured (GCS≤8) and receiving phenytoin did more poorly on most neuropsychological measures than controls determined by the overall rank-sum type test

Author, Year Country Study Design Sample Size	Methods	Outcome
	Outcome Measure: Halstead–Reitan Neuropsychological Test Battery, Katz Adjustment Scale, Sickness Impact Profile.	at 1mo ($p<0.05$). No significant differences were found at 1yr. 3. No significant differences in neuropsychological performance were found between groups for patients with moderate injuries (GCS≥9) at 1mo or 1yr. 4. Changes in neuropsychological measures from 12 to 24mo showed that phenytoin had a small but negative widespread cognitive effect as evidenced by the overall rank-sum type test ($p<0.05$).
Temkin et al. (1990) USA RCT PEDro=6 $N_{Initial}$=404, N_{Final}=123	**Population:** TBI; *Phenytoin Group (n=208):* Mean Age=34yr; Gender: Male=162, Female=46; GCS ≤10=125. *Placebo Group (n=196):* Mean Age=34yr; Gender: Male=147, Female=49; GCS ≤10=131. **Treatment:** Participants were randomized to either the phenytoin (n=208) or placebo group (n=196). The phenytoin group received an initial dose of 20 mg/kg intravenously, then serum levels were maintained at 3–6 µmol/l. Treatment started within 24hr of injury and continued for 1yr. Follow up at 2yr. **Outcome Measure:** Occurrence of early (<1wk) and late (>8d) seizures.	1. Cumulative early seizure rates were 3.6% in the phenytoin group and 14.2% in the control group ($p<0.001$); phenytoin was associated with a decrease of 73% in the risk of early seizures. 2. Late seizure occurrence (day 8 to 2yr) did not differ significantly between the treatment and control groups (27.5% vs 21.2%, $p>0.2$). 3. More participants in the phenytoin group stopped taking the drug between day 8 and 1yr, mainly due to idiosyncratic reactions or requests (103 vs 67).
Young et al. (1983) USA RCT PEDro=6 N=244	**Population:** TBI; *Phenytoin Group (n=136):* Mean Age=24.4yr; Gender: Male=110, Female=26. *Placebo Group (n=108):* Mean Age=25.8yr; Gender: Male=91, Female=71. **Treatment:** Patients were administered phenytoin (serum concentration 10-20µg/ml) or placebo, starting within 24hr of injury. **Outcome Measure:** Occurrence of early seizures (≤1wk of injury).	1. Five in the phenytoin group and 4 in the control group had early seizures ($p=0.75$). Mean time from injury to early seizure in the treatment and control group was 3.2 and 4.5d, respectively ($p=0.41$).
Young et al. (1983) USA RCT PEDro=6 $N_{Initial}$=214, N_{Final}=179	**Population:** TBI; *Phenytoin Group (n=105):* Mean Age=24.1yr; Gender: Male=84, Female=21. *Placebo Group (n=74):* Mean Age=26.3yr; Gender: Male=61, Female=13. **Treatment:** Participants were treated with phenytoin (serum concentration 10-20µg/ml) or placebo starting within 24hr of injury. Treatment duration was 18mo. Participants were switched to phenobarbital if there was a hypersensitivity to phenytoin (n=20). **Outcome Measure:** Occurrence of late (>7d post-injury) seizures.	1. Late seizures occurred in 11 (12.9%) of the phenytoin group, 2 (10%) of the phenobarbital group, and 8 (10.8%) of controls. There were no significant differences between groups in terms of the percentage of participants with late seizures ($p=0.75$).

Author, Year Country Study Design Sample Size	Methods	Outcome
McQueen et al. (1983) United Kingdom RCT PEDro=7 N=164	**Population:** TBI; *Phenytoin Group (n=84)*: Gender: Male=67, Female=17; Age Range: 5-15yr=29, 16-65yr=55. *Placebo Group (n=80)*: Gender: Male=63, Female=17; Age Range: 5-15yr=14, 16-65yr=66. **Treatment:** Patients received either phenytoin or placebo for 1yr. Phenytoin administration for adults was 300mg and for children 5mg/kg. Follow-up continued for 2yr. **Outcome Measure:** Occurrence of seizures.	1. Only 48% of the treatment group had plasma levels greater than 40µmol/l (concentrations of 40-80 µmol/l were considered therapeutic). 2. Nine percent of participants developed post-traumatic epilepsy within the first 2yr. 3. At 1yr, 6 participants in the treatment group and 5 in the control group developed post-traumatic epilepsy. 4. Eight participants in the treatment group and 7 in the control group developed seizures by 2yr.
Gul et al., (2019) Pakistan Cohort $N_{Initial}$=163, N_{Final}=163	**Population:** TBI=163; IV phenytoin started within 12hr of injury, n=91; IV phenytoin started after 12hr, n=72; Mean Age= 24.69±10.186yr; Gender: Male=122, Female=41; Time Post-Injury=Acute; Severity: Severe=83, Moderate=80. **Treatment:** Participants with moderate to severe TBI were started on IV phenytoin at admission for seizure prophylaxis. Seizure incidence in participants given phenytoin within 12hr or after 12hr of TBI were compared. Outcomes were monitored over the first 7d of recovery. **Outcome Measure:** Early seizure incidence.	1. Patients given prophylactic IV phenytoin within 12hr of moderate to severe TBI had significantly lower incidence of seizure (p=.018) during the first 7 days compared with patients given IV phenytoin after 12hr of TBI.
Bhullar et al. (2014) USA Case Control N=93	**Population:** TBI, GCS=3-8; *No Prophylaxis Group (n=43)*: Gender: Male=28, Female=15. *Phenytoin Prophylaxis Group (n=50)*: Gender: Male=42, Female=8. **Treatment:** Medical records were reviewed, and patients were divided into two groups: no prophylaxis and phenytoin prophylaxis. **Outcome Measure:** Occurrence of early (<7d post-injury) seizures, length of stay (LOS), Glasgow Outcome Scale (GOS), modified Rankin Scale (mRS).	1. There was no significant difference in the occurrence of early seizures between the no prophylaxis and phenytoin groups (2.3% versus 4.0%, p=1.0). 2. The phenytoin group, compared to no prophylaxis, had longer hospital stays (36± 31 vs 25± 16d, p=0.03), and worse functional outcome at discharge (GOS, 2.9± 1.0 versus 3.4±1.1, p=0.01; mRS, 3.1± 1.5 versus 2.3±1.7, p=0.02).
Sabo et al. (1995) United States Case series N=98	**Population**: ABI; Chronic subdural hematoma (CSH); head trauma=77.5%; Mean age=71.8; Gender: Male=65, Female=33. **Intervention:** Retrospective analysis of individuals treated surgically for CSH. 46% of participants received prophylactic phenytoin. ACM prophylaxis included an initial dose of phenytoin (15mg/kg) intravenously or by mouth. All 98 participants underwent at least one surgical intervention for CSH, Burr holes=85, twist-drills=13. **Outcome Measures:** Prevalence of seizures.	1. The onset of new seizures was found in 18.5% of individuals and was associated with increased mortality (P <0.005) and morbidity (P <0.036). 2. A significant decrease in the onset of new seizures seen in the group who received ACM compared to those without the administration phylactic ACM (P = <0.001). 3. Phenytoin was associated with dermatological complications.
Wohns et al. (1979) United States	**Population:** Head Trauma; Mean Age=29 ± 19yr, Gender: Male=47, Female=15	1. Of the 50 participants who received phenytoin prophylaxis, five (10%) developed LPTS.

Author, Year Country Study Design Sample Size	Methods	Outcome
Case series N=62	**Intervention:** Administration of phenytoin as prophylaxis with serum level goal of 10-20 $\mu g/ml$. **Outcome Measures:** Incidence of LPTS in participants treated prophylactically with phenytoin only.	2. Of the 12 participants who did not receive prophylaxis, six (50%) developed LPTS.
Young et al. (1979) United States Pre-Post N=84	**Population:** Severe TBI; Mean Age: 24yr, 62% over the age of 16; Gender: Male=63, Female=21 **Intervention:** Prophylactic phenytoin regimen with plasma concentrations maintained at 10-20 µg/ml throughout the study period. **Outcome Measures:** Incidence of post-traumatic seizures between 1 week and 1 year after injury.	1. Only 1/3 (n=30) of the participant population continued to take phenytoin after the first month. 2. Five participants (6%) had seizures between 1 and 52 weeks after their severe head injuries, and one participant experienced seizures on more than one occasion. 3. There was a reduced incidence of seizures throughout the first year, despite low rate of long-term compliance, suggesting that phenytoin has a prophylactic effect.

Discussion

There is conflicting evidence on the effect of phenytoin on the occurrence of early seizures. In two studies – one RCT and one case control study – the authors did not find phenytoin to be effective (Bhullar et al., 2014; Young et al., 1983). However, in an RCT, Temkin et al., (1990) found that phenytoin reduced the rate of early seizures compared to placebo. The efficacy of phenytoin for the prophylaxis of seizures was also reported by Wohns et al. (1979) and by Sabo et al. (1995) in a case series studies and by Young et al. (1979) in a pre-post study. Furthermore, in a cohort study, Gul et al., (2019) found that early administration of phenytoin (<12 hours) post-TBI reduced the incidence of early post-traumatic seizures when compared to later administration (>12 hours). According to a systematic review by Thompson et al. (2015), treatment with phenytoin decreased the risk of early seizure compared to placebo or standard care; however, the authors indicated that the evidence is mostly low-quality. In clinical practice, the use of AEDs, such as phenytoin is recommended during the first 7 days post-injury to reduce the incidence of early post-traumatic seizures (INESSS-ONF, 2015).

In three RCT studies, phenytoin was no more effective than placebo in preventing the onset of late seizures, when started acutely post-TBI and continued for 12 to 18 months (McQueen et al., 1983; Temkin et al., 1990; Young et al., 1983). Similar results were reported by Thompson et al. (2015) in a systematic review. It should also be noted that phenytoin has been shown to have a negative impact on cognition (1991). Further, those taking phenytoin have been shown to have longer hospital stays and worse functional outcomes at discharge than individuals receiving no treatment (Bhullar et al., 2014). Overall, given the lack of evidence for benefit and the potential for harm, the continuation of AED prophylaxis beyond 7 days post-injury may not recommended (INESSS-ONF, 2015).

Conclusions

There is level 1b evidence that early administration of phenytoin may be effective in reducing the rate of early post-traumatic seizures in individuals with TBI (Temkin et al., 1990; Gul et al., 2019; Wohns et al., 1979; Young et al., 1979).

There is level 1b evidence (McQueen et al., 1983; Temkin et al., 1990; Young et al., 1983) that phenytoin may not be more effective than placebo in preventing late seizures post TBI.

There is level 3 evidence (Bhullar et al., 2014) that phenytoin may negatively impact recovery when compared to a placebo in patients with TBI.

There is level 4 evidence (Sabo et al., 1995) that prophylaxis using phenytoin may decrease occurrence of seizures in individuals treated surgically for chronic subdural hematoma.

KEY POINTS

- Phenytoin, when compared to placebo, may be effective for the prophylaxis of early post-traumatic seizures; however, it may not prevent the onset of late seizures in individuals with TBI.

Fosphenytoin

Fosphenytoin is a water-soluble prodrug of phenytoin (Aleyadeh & Carson, 2022). Intravenous fosphenytoin is preferred in situations that require rapid administration (Eriksson et al., 2009). There is limited evidence on the use of fosphenytoin in individuals with brain injuries.

TABLE 7 | Fosphenytoin for the Prophylaxis of Post-Traumatic Seizures

Author, Year Country Study Design Sample Size	Methods	Outcome
Arai et al. (2018) Japan Cohort N=105	**Population:** TBI; Mean Age=64.9yr; Gender: Male=56, Female=49; Mean GCS=11.3±1.72 **Treatment:** Patients received either carbamazepine (200 mg/day) if oral route was available or fosphenytoin (7.5mg/kg/day) if it was not. Patients were divided based on EEG findings into three groups within 72hrs of admission: epileptiform EEG group (n=23) received adjuvant levetiracetam (1000 mg/day) with prophylactic therapy; nonepileptiform EEG group (n=18) continued admission therapy; no EEG group (n=64) discontinued admission therapy after 7 days. Repeated short-duration EEG measurements (20-30min) were	1. On admission, prophylactic administration of an antiepileptic drug was initiated in all individuals; convulsive seizures occurred in 10 patients, eight of whom had interictal epileptiform abnormalities on EEG, a total of 31 patients did not have seizures and were suspected to have non-convulsive epilepsy. 2. None of the patients (n=105) experienced recurrent or new-onset post-traumatic epilepsy after EEG monitoring and combined pharmaceutical intervention.

Author, Year Country Study Design Sample Size	Methods	Outcome
	performed daily for the epileptiform EEG and non-epileptiform EEG groups for 14 days. **Outcome Measures:** Incidence of seizures as measured by abnormal EEG.	

Discussion

In one case series study, Arai et al. (2018) examined the prophylactic administration of fosphenytoin or carbamazepine. Individuals were treated with either fosphenytoin, if the oral route was not available or carbamazepine if it was. In individuals were classified into three groups, 23 patients in the epileptiform EEG group, 18 patients in the non-epileptiform EEG group and 64 patients in the no EEG group. In the first group, individuals received an adjuvant antiepileptic drug, the second group maintained antiepileptic therapy and the third group discontinued the therapy. At 14 days, none of the patients had recurrent seizures, suggesting that the acute management system was effective for the prevention of early PTE.

Conclusions

There is level 2 evidence (Arai et al., 2018) that administration of fosphenytoin or carbamazepine, with continuous EEG monitoring, may be effective for the prophylaxis of early post-traumatic seizures in individuals with TBI.

KEY POINTS

- The administration of fosphenytoin or carbamazepine with continuous EEG monitoring may be effective for the prevention of early post-traumatic seizures.

Levetiracetam

Levetiracetam is an anticonvulsant used for focal or generalized myoclonic and tonic-clonic seizures (Howard et al., 2018). Levetiracetam has also been used in brain injuries, including those of traumatic etiology. The majority of the studies have examined the effectiveness of levetiracetam when compared to phenytoin.

TABLE 8 | Levetiracetam for the Prophylaxis of Post-Traumatic Seizures

Author, Year Country Study Design Sample Size	Methods	Outcome
Human et al. (2018)	**Population:** Patients with subarachnoid hemorrhage (SAH); Brief levetiracetam (LEV)	1. One patient in the extended LEV group experienced an in-hospital seizure

Author, Year Country Study Design Sample Size	Methods	Outcome
USA RCT PEDro= 8 N=84	group (n=35): Mean Age=52±15yr; Gender: Male=12, Female=23. Extended LEV group (n=49): Mean Age=60±14yr; Gender: Male=17, Female=32. **Treatment:** All patients received an initial IV dose of LEV (1000 mg) on admission and continued LEV (1000 mg BID) for 3 days. Patients were then randomized to discontinue LEV (n=35) or to continue until hospital discharge (1000-mg BID) (n=49). **Outcome Measures:** Occurrence of seizures (in-hospital), Modified Rankin Score (mRS) at follow-up (3mo-1yr after discharge)	compared to 3 in the brief LEV group (2% vs 9%, p=0.20). 2. There was a relative reduction of seizures in the extended LEV group vs brief LEV group by 76%. 3. Good functional outcome after discharge (mRS 0-2) was more likely in the brief LEV group (83% vs 61%, p=0.04).
Patanwala et al. (2016) United States Cohort $N_{initial}$=206, N_{final}= 169	**Population:** TBI; Participants with TBI who received *Levetiracetam 500 mg, n=206:* Mean Age=48yr; Gender: Male=131; Female=38; Mean GCS=5. **Intervention:** Retrospective review of levetiracetam 500 mg intravenously (n=147, 87%) or via the enteral route (n=22, 13%) every 12 hours. Median Time from injury to levetiracetam initiation=3.5h (IQR 1-13). **Outcome Measures:** Occurrence of seizure within 7 days of TBI.	1. Occurrence of seizure was low in this trial evaluating a lower dose of levetiracetam. Four participants had a seizure (n=4, 2.4%) within the first 7 days of hospitalization. 2. There was no significant difference between the seizure rate observed in this study and a hypothesized value of 3.6% based on a previous trial of phenytoin.
Levetiracetam versus Phenytoin		
Younus et al. (2018) Pakistan RCT PEDro= 6 N = 140	**Population:** *Phenytoin Group (N=69)*: Mean GCS=11.23. *Levetiracetam group (N=73):* Mean GCS=11.17. *Overall:* 117 males, 23 females; Mean Age=29.48±16.24y **Treatment:** TBI patients admitted to the hospital were randomized into the phenytoin or levetiracetam groups. The first dose of medication was given within 24h of injury. Both groups received medication for 7 days. No statistical differences existed between groups at baseline. **Outcomes:** Abnormal EEG (EEGs were completed the 1st day post trauma and on day 7 of treatment), Seizure activity (7-10 days), Glasgow Coma Scale (GCS).	1. The number of abnormal EEGs was found to be significantly different between the two groups (p=0.002); the levetiracetam group had fewer individuals with abnormal EEG. 2. The amount of seizure activity at follow-up was significantly different between groups (p=0.014); the levetiracetam group had fewer instances of seizures. 3. There was no significant difference between GCS scores at follow-up between the two groups.
Khan et al. (2016) Pakistan RCT PEDro=5 N=154	**Population**: TBI; Mean Age=24.15yr; Gender: Male=115, Female=29; Mean GCS: 59.1% (8-13), 40.9% (3-7). **Treatment:** Group A received phenytoin starting in a loading dose of 20mg/kg intravenously over 60min, followed by a maintenance dose of 5 mg/kg/day; Group B received levetiracetam starting in a loading dose of 20m/kg intravenously over sixty minutes followed by maintenance dose of 10-	1. There were no significant differences between treatment groups in terms of the incidence of post-traumatic seizures. 2. There was no significant difference in how each drug impacted moderate vs severe TBI and seizure rates.

Author, Year Country Study Design Sample Size	Methods	Outcome
	20 mg/kg/day. All patients were followed for seven days. **Outcome Measure:** Incidence of post-traumatic seizures, efficacy of drug on moderate vs severe TBIs.	
Szaflarski et al. (2010) USA RCT PEDro=8 N=52	**Population:** TBI=46; SAH=6; *Phenytoin group (PHT; n=18):* Mean Age=35yr; Gender: Male=13, Female=5; Mean GCS=4. *Levetiracetam group (LEV; n=34):* Mean Age=44yr; Gender: Male=26, Female=8; Mean GCS=5. **Treatment:** Patients were randomized within 24h of injury. Patients received either a loading dose of intravenous PHT 20mg/kg, then 5mg/kg/d or intravenous LEV at 20mg/kg, and then 1000mg every 12hr for 7d. **Outcome Measure:** Occurrence of early seizures, Glasgow Outcome Scale (GOS), GOS-Extended (GOSE), Disability Rating Scale (DRS), Resource Utilization Questionnaire.	1. There were no significant differences in the occurrence of early seizures between the PHT and LEV groups (3 versus 5, p=1.0) 2. There were no significant between-group differences in GOS at discharge (p=0.33) and 6mo post-discharge (p=0.89). 3. There were no significant differences in the occurrence of fever, increased intracranial pressure, stroke, hypotension, arrhythmia, renal/liver abnormalities, or death between the two groups (p>0.15 for all). 4. Compared to the LEV group, those in the PHT group experienced a significant worsening of their neurological status more often (p=0.024), and experienced anemia less often (p=0.076). 5. Compared to PHT group, the LEV group showed significantly lower DRS at 3 and 6mo (p=0.006 and p=0.037), and higher GOS-E at 6mo (p=0.016) in patients who survived. 6. The presence of focal slowing, epileptiform discharges, and seizures were not predictive of outcome (GOS-E, DRS). More severe slowing was positively associated with DRS and negatively associated with GOS-E at discharge, 3 and 6 mo.
Steinbaugh et al. (2012) USA Addition to Szaflarski et al. 2010 RCT	**Addition**: Patients received continuous video EEG (cEEG) for up to 72h which was compared to the outcomes collected.	
Javed et al. (2016) Pakistan Cohort N=100	**Population:** TBI; *Group 1 (n=50):* Mean Age=31.16yr. *Group 2 (n=50)*: Mean Age=34.96. Gender: Not Reported. **Treatment:** Group 1: given IV phenytoin load then switched to oral levetiracetam (35 mg/kg/dose three times daily) by 72h. Group 2: cohort of patients in a database that were given IV phenytoin load then kept on phenytoin during the same time period. Patients were followed for 7 days. **Outcome Measure:** Incidence of post-traumatic seizures as measured by EEG (patients with clinical seizure, mental state change or deep coma underwent EEG).	1. There was no significant difference between the two treatment groups in terms of incidence of early post-traumatic seizures.
Radic et al. (2014) USA Case Control N=288	**Population:** Subdural Hematoma; *Levetiracetam group (LEV; n=164):* Mean Age=65.96yr; Gender: Male=98, Female=66; Mean GCS=13.5. *Phenytoin group (PHT; n=124):*	1. There was no significant difference between LEV and PHT in clinical or electrographic seizure risk for patients without a midline shift. 2. In individuals with midline shift >0 mm, LEV was associated with an increased risk of

Author, Year Country Study Design Sample Size	Methods	Outcome
	Mean Age=62yr; Gender: Male=85, Female=39; Mean GCS=12.7. **Treatment:** Patients were retrospectively analyzed. Those who received LEV were compared to those who received PHT for seizure prophylaxis. **Outcome Measure:** Seizure rate and adverse drug events.	electrographic seizures during hospitalization (p=0.028) and a decreased risk of adverse drug effects (p=0.001), compared with PHT use.
Gabriel & Rowe (2014) USA Cohort N=19	**Population**: TBI; *Phenytoin Group (PHT, n=14):* Mean Age=46.8yr; Gender: Male=10, Female=4; Mean GCS=3. *Levetiracetam Group (LEV, n=5):* Mean Age=48.8yr; Gender: Male=3, Female=2; Mean GCS=14. **Treatment:** Participants were divided based on prophylactic treatment: PHT or LEV. Follow-up interviews were conducted. **Outcome Measure:** Glasgow Outcome Scale-Extended (GOS-E) >/= 6mos post-injury administered by telephone, occurrence of early and late seizures, medication-related complications.	1. The LEV group had a statistically higher median GCS at presentation (p=0.016) and ICU discharge (p=0.044), compared to the PHT group. The PHT group, compared to the LEV group, had a longer period of time between injury and GOS-E assessment (808.8 versus 484.4d, p=0.001). 2. There was no significant difference in the mean GOS-E scores at follow-up (PHT 5.07 versus LEV 5.60, p=0.58). 3. There was no significant difference between groups for occurrence of early or late seizures (both p=0.53). 4. Compared to the PHT group, the LEV group was significantly less likely to experience medication-related complications (p=0.038); the PHT group had a significantly higher rate of days with fever (p=0.014).
Inaba et al. (2013) USA PCT N=813	**Population:** TBI; *Levetiracetam Group (LEV, n=406):* Mean Age=51.7yr; Gender: Male=300, Female=106; Mean GCS=12.1. *Phenytoin Group (PHT, n=407):* Mean Age=53.6yr; Gender: Male=280, Female=127; Mean GCS=12.6. **Treatment:** Participants were administered either LEV at 1000mg every 12h or PHT. In the PHT group the loading dose was 20mg/kg then 5mg/kg/d every 8h. Treatment lasted 7d. **Outcome Measure:** Seizure occurrence.	1. There was no significant difference in seizure rates between groups (1.5% versus 1.5%, p=0.997). 2. There were no significant differences between groups (LEV vs. PHT) in terms of adverse drug reactions (7.9% versus 10.3%, p=0.227), complications (28.3% versus 27.0%, p=0.679) or mortality rates (5.4% versus 3.7%, p=0.236).
Caballero et al. (2013) USA Case Control N=90	**Population:** TBI; Levetiracetam group (n=18): Mean Age=57yr; Gender: Male=14, Female=4; Median GCS=6. Phenytoin group (n=72): Mean Age=45yr; Gender: Male=54, Female=18; Median GCS=5. **Treatment:** Patients who received levetiracetam (median loading dose=1000 mg, median maintenance dose=500 mg/12hr) for post-traumatic seizure prophylaxis were compared retrospectively to those who received phenytoin (median loading dose=13mg/kg, median maintenance dose=4mg/kg/day).	1. Seizure activity prevalence was similar for both the levetiracetam and phenytoin groups (28% vs 29%, p=0.99). 2. ICU length of stay (13 vs 18 days, p=0.28) and time to seizure activity (4 vs 6 days, p=0.24) were also similar between groups.

Author, Year Country Study Design Sample Size	Methods	Outcome
	Outcome Measures: Occurrence of seizure as measured by EEG activity, ICU length of stay, additional AED administration	
Kruer et al. (2013) USA Cohort N=109	**Population:** TBI; Median GCS=5. *Phenytoin Group (PHT, n=89):* Median Age=43.1yr; Gender: Male=76, Female=13. *Levetiracetam Group (LEV, n=20):* Median Age=34.1yr; Gender: Male=19, Female=1. **Treatment:** Retrospective review of patients administered PHT or LEV. **Outcome Measure**: Occurrence of early seizures.	1. One patient from each group seized in the first 7d (p=0.335). 2. Hospital length of stay did not differ significantly between groups (median days, LEV 26.5 versus PHT 11, p=0.134).
Jones et al. (2008) USA Cohort N=27	**Population:** Severe TBI; Age groups: <25yr=8, 26-35=8, 26-45=5, >46=6; Gender: Male=20, Female=7. **Treatment:** Patients received levetiracetam (n=15; 500mg IV every 12h for 7d) administered within 24hr of injury and were compared to a retrospective cohort of patients who received phenytoin (n=12). **Outcome Measure:** Occurrence of early seizures.	1. There was a significant difference in the occurrence of abnormal EEG findings (seizure or seizure tendency with epileptiform activity) between groups (p= 0.003), with the levetiracetam group having more abnormal findings. 2. There was no significant difference between groups for actual seizures (p=0.556).

Discussion

In an RCT, Human et al. (2018) compared brief levetiracetam treatment (three days duration) to extended treatment which was continued until hospital discharge; the authors found a relative reduction of seizures by 76% in the group that received the extended treatment protocol. Seizure occurrence was also reported to be low (2.4%) during the initial 7 days post hospitalization in a cohort study by Patanwala et al. (2016) using a lower dose of levetiracetam (500 mg BID).

When phenytoin was compared to levetiracetam, many studies have shown no difference between the two drugs in terms of seizure rates (Inaba et al., 2013; Javed et al., 2016; Jones et al., 2008; Kruer et al., 2013; J. A. Radic et al., 2014), complications, adverse drug reactions, mortality rates (Inaba et al., 2013), lengths of hospital stay (Kruer et al., 2013), and injury severity (Khan et al., 2016). Similarly, in an RCT, Szaflarski et al. (2010) found no difference in early seizure rates, death, or adverse events when comparing the two drugs; however, the authors found that individuals on levetiracetam performed significantly better on the Disability Rating Scale at 3 and 6 months, and the GOS at 6 months post-intervention compared to those who received phenytoin.

In an RCT by Younus et al. (2018), individuals on levetiracetam had a significant decrease in seizure activity at follow-up, and fewer abnormal EEGs compared to those on phenytoin. In a cohort study, Gabriel and Rowe (2014) found no significant difference in the occurrence of late seizures when

comparing levetiracetam and phenytoin. Furthermore, Radic et al. (2014) found that individuals with evidence of a midline shift were at a higher risk for electrographic seizures and a lower risk for adverse drug reactions on levetiracetam compared to phenytoin

In a meta-analysis, Zafar et al. (2012) concluded that there was no superiority of either drug in terms of preventing early seizures. Similarly, a systematic review and meta-analysis by Yang et al. (2016) concluded that levetiracetam was not superior to phenytoin in terms of safety or efficacy for prophylaxis of early or late PTS; however, no class I evidence was identified. In clinical practice, phenytoin and levetiracetam are the AEDs most commonly prescribed during the first week post-injury for the prophylaxis of early post-traumatic seizures (INESSS-ONF, 2015).

Conclusions

There is level 1b evidence (Human et al., 2018) that levetiracetam may reduce the occurrence of in-hospital seizures in individuals with ABI.

There is level 1b evidence (Szaflarski et al., 2010; Steinbaugh et al., 2012), level 2 evidence (Inaba et al., 2013; Gabriel & Rowe, 2014; Javed et al., 2016; Jones et al., 2008; Kruer et al., 2013; Khan et al., 2016; Patanwala et al., 2016) and level 3 evidence (Radic et al., 2014) that there is no significant difference in the rate of early post-traumatic seizures when comparing phenytoin to levetiracetam in patients with ABI.

There is level 2 evidence (Gabriel & Rowe, 2014) that phenytoin is not more effective in reducing the rate of late post traumatic seizures compared to levetiracetam in patients with ABI.

There is level 1b evidence (Younus et al., 2018) that levetiracetam is more effective than phenytoin for the reduction of seizures at 7-10 days post-injury in patients with moderate to severe TBI.

There is level 3 evidence (Radic et al., 2014) that levetiracetam may be associated with a higher risk for electrographic seizures compared to phenytoin among patients with midline shift.

KEY POINTS

- Extended treatment with levetiracetam may be effective for the reduction of in-hospital seizures in individuals with ABI.
- Levetiracetam may be as effective as phenytoin in the prevention of early post-traumatic seizures.

Carbamazepine

Carbamazepine is an anticonvulsant drug that is often used for the treatment of seizure disorders and conditions such as neuropathic pain and bipolar disorder (Alrashood, 2016). There is limited evidence

on the use of carbamazepine for the prophylaxis of post-traumatic seizures in individuals with brain injuries.

TABLE 9 | Carbamazepine for the Prophylaxis of Post-Traumatic Seizures

Author, Year Country Study Design Sample Size	Methods	Outcome
Arai et al. (2018) Japan Cohort N=105	**Population:** TBI; Mean Age=64.9yr; Gender: Male=56, Female=49; Mean GCS=11.3±1.72 **Treatment:** Patients received either carbamazepine (200 mg/day) orally or fosphenytoin (7.5mg/kg/day) intravenously on admission. Patients were divided based on EEG findings into three groups within 72hrs of admission: epileptiform EEG group (n=23) received adjuvant levetiracetam (1000 mg/day) with prophylactic therapy; nonepileptiform EEG group (n=18) continued admission therapy; no EEG group (n=64) discontinued admission therapy after 7 days. Repeated short-duration EEG measurements (20-30min) were performed daily for the epileptiform EEG and non-epileptiform EEG groups for 14 days. **Outcome Measures:** Incidence of seizures as measured by abnormal EEG.	1. None of the patients (n=105) experienced recurrent or new-onset post-traumatic epilepsy after EEG monitoring and combined pharmaceutical intervention.

Discussion

In one case series study, Arai et al. (2018) examined the prophylactic administration of fosphenytoin or carbamazepine. Individuals were treated with either fosphenytoin, if the oral route was not available or carbamazepine if it was. In individuals were classified into three groups, 23 patients in the epileptiform EEG group, 18 patients in the non-epileptiform EEG group and 64 patients in the no EEG group. In the first group, individuals received an adjuvant antiepileptic drug, the second group maintained antiepileptic therapy and the third group discontinued the therapy. At 14 days, none of the patients had recurrent seizures, suggesting that the acute management system was effective for the prevention of early PTE.

Conclusions

There is level 2 evidence (Arai et al., 2018) that administration of fosphenytoin or carbamazepine, with continuous EEG monitoring, may be effective for the prophylaxis of early post-traumatic seizures in individuals with TBI.

KEY POINTS

- The administration of fosphenytoin or carbamazepine with continuous EEG monitoring may be effective for the prevention of early post-traumatic seizures.

Lacosamide

Lacosamide is an anticonvulsant that has been used as 'add-on therapy' for the treatment of focal seizures, as well as for the treatment of seizures in individuals who present with drug-resistant epilepsy (Babar et al., 2021). There is limited evidence on the use of lacosamide in individuals with brain injuries.

TABLE 10 | Lacosamide for the Prophylaxis of Post-Traumatic Seizures

Author, Year Country Study Design Sample Size	Methods	Outcome
Lacosamide versus Phenytoin		
Kwon et al., (2019) USA Cohort $N_{Initial}$=481, N_{Final}=481	**Population:** TBI=481; *Phenytoin Group (n=116):* Mean Age=50±21yr; Gender: Male=82, Female=34; Time Post-Injury=Acute; Severity: Mean GCS=11.3±4.3. *Lacosamide Group (n=365):* Mean Age=58±22yr; Gender: Male=242, Female=123; Time Post-injury=Acute; Severity: Mean GCS=12.5±3.8. **Treatment:** Lacosamide (50mg 2/d for 7d if GCS=13-15; 200mg once, followed by 100mg 2/d for 7d if GCS <13) versus phenytoin (loading dose: 15-20mg/kg; 300-400mg/d for 7d). **Outcome Measures:** Incidence of early post-traumatic seizures, adverse events.	1. No significant difference in early post-traumatic seizure incidence was observed between groups (p>.05). 2. The incidence of adverse events was significantly higher in the phenytoin group compared to the lacosamide group (p=.03).

Discussion

In a cohort study, Kwon et al. (2019) examined the efficacy of lacosamide versus phenytoin for seizure prophylaxis post TBI. The authors found that lacosamide and phenytoin were equally effective in preventing early post-traumatic seizures; however, the incidence of adverse events was significantly higher in the phenytoin group. This is in line with the previously mentioned research that suggests phenytoin can impair recovery as well as lead to longer hospital stays and worse functional outcomes (Bhullar et al., 2014).

Conclusions

There is level 2 evidence (Kwon et al., 2019) that lacosamide may be as effective as phenytoin for the prophylaxis of post-traumatic seizures; however, lacosamide may have a more favourable side effect profile in patients with TBI.

KEY POINTS

- Lacosamide may be as effective as phenytoin for post-traumatic seizure prophylaxis with better tolerability; however, more research is needed.

Valproic Acid

Valproic acid is an anticonvulsant that has been used for the treatment of seizures and bipolar disorder (Zhu et al., 2017). Valproic acid has also been used for the management of migraine, and some studies have reported a possible effect of this medication on specific types of cancer (Singh et al., 2021).

TABLE 11 | Valproic Acid for the Prophylaxis of Post-Traumatic Seizures

Author, Year Country Study Design Sample Size	Methods	Outcome
Ma et al. (2010) China Cohort N=159	**Population:** TBI; Age: ≤18yr=7, 19-60yr=129, >60yr=23; Gender: Male=122, Female=37. **Treatment:** Retrospective review; TBI patients treated with sodium valproate (n=35) injections (1-3 days after TBI, 10-15 mg/kg/day) were compared to patients who received no therapy (7-day period). **Outcome Measures:** Occurrence of seizures (within 7 days)	1. There was no significant difference in the occurrence of posttraumatic seizures in the sodium valproate group (n=35) vs control (n=124) (0 v 4.4%, p>0.05). 2. There was no significant difference in the occurrence of posttraumatic seizures in the severe TBI subgroup who received sodium valproate (n=20) vs no treatment (n=67) (0 vs 6.9%, p>0.25).
Valproic Acid versus Phenytoin		
Dikmen et al. (2000) USA RCT PEDro=8 $N_{Initial}$=279, N_{Final}=107	**Population:** TBI; Gender: Male=228, Female=51. *Group 1 (n=94)*: Mean Age=37.14yr; Mean GCS=11.3. *Group 2 (n=91)*: Mean Age=36.58yr; Mean GCS=11.23. *Group 3 (n=94)*: Mean Age=35.85yr; Mean GCS=12.11. **Treatment:** Patients were randomized into three groups within 24h of injury: 1) valproic acid (VPA) for 1mo then 5mo of placebo; 2) VPA for 6mo; and 3) phenytoin (PHT) for 1wk then placebo until 6mo post-injury. **Outcome Measure:** A battery of neuropsychological measures.	1. There was a trend towards a higher mortality rate in the VPA groups compared to the PHT group (p=0.07). 2. There were no significant differences at 1, 6 or 12mo on the composite neuropsychological measures, or on only the cognitive measures (0.551<p<0.812). 3. No individual neuropsychological measure showed a significant difference between the treatment groups at 1-, 6- or 12-months post-injury.
Temkin et al. (1999) USA RCT PEDro=7 $N_{Initial}$=379, N_{Final}=283	**Population:** TBI; Gender: Male=310, Female=69. *Phenytoin Group (n=132):* Mean Age=36yr; Mean GCS=11.7. *Valproate (1mo, n=120):* Mean Age=40yr; Mean GCS=11.6. *Valproate (6mo, n=127):* Mean Age=36yr; Mean GCS=11.1. **Treatment:** Patients were divided into three groups within 24h of injury: (1) phenytoin for 1wk (20mg/kg then 5mg/kg/d), placebo until 6mo post-injury; (2) Valproate (20mg/kg, then 15mg/kg/d) for 1mo, placebo for 5mo; or (3) Valproate for 6mo. Follow-up continued for 2yr. **Outcome Measure:** Incidence of early and late (>7d post-injury) seizures, mortality rates.	1. There was no significant difference in the number of early seizures between the combined valproate (4.5%) and phenytoin (1.5%, p=0.14) groups. 2. There was no significant difference between groups (p=0.19) in the occurrence of late seizures. 3. Late seizures occurred in 11, 17, and 15 participants in the 1mo and 6mo valproate groups and the phenytoin group, respectively. 4. There were no significant differences in mortality rates between groups (7.2% phenytoin versus 13.4% in the combined valproate group, p=0.07). 5. In the phenytoin group, a participant had a rash requiring medication at 1wk and in the valproate (6mo) group a participant had a low neutrophil count at 2-4wk, both thought to be treatment related.

Discussion

In a cohort study, Ma et al. (2010) compared valproic acid to no therapy for seizure prophylaxis among persons with TBI; the authors found no significant difference in the occurrence of EPTS between the treatment group and control group. Two studies compared valproic acid to phenytoin. When examining the effects of phenytoin compared to valproate, an RCT by Temkin et al. (1999) found no significant differences in rates of early seizures, late seizures, or mortality. In another RCT, Dikmen et al. (2000) found no significant differences on measures of cognition when comparing persons with TBI receiving valproic acid to those given phenytoin for seizure prophylaxis.

Conclusions

There is level 1b evidence (Temkin et al., 1999; Dikmen et al., 2000) that the valproic acid and phenytoin may have similar efficacy for the prophylaxis of both early and late seizures following TBI.

There is level 2 evidence (Ma et al., 2010) that valproic acid may not be effective for the prevention of early post-traumatic seizures when compared to no therapy.

KEY POINTS

- Valproic acid may not be effective in for the prevention of post-traumatic seizures when compared to no treatment during the first seven days post injury.
- Valproic acid and phenytoin may have similar effectiveness for the prophylaxis of early and late seizures.

Barbiturates

Barbiturates are sedatives that have been commonly prescribed to treat intracranial pressure in individuals with brain injuries, as they slow down brain action and reduce fluid production (Roberts & Sydenham, 2012).

Phenobarbital

Phenobarbital is a barbiturate that is frequently used to treat neonatal and childhood seizure disorders, as well as drug-resistant convulsive and nonconvulsive status epilepticus (Brodie & Kwan, 2012). Phenobarbital has a wide range of side effects, including behavioural problems, sedation, impaired cognition and depression (Brodie & Kwan, 2004).

TABLE 12| Phenobarbital For the Prophylaxis of Post-Traumatic Seizures

Author, Year Country Study Design Sample Size	Methods	Outcome
Manaka (1992) Japan RCT PEDro=3 $N_{Initial}$=244, N_{Final}=191	**Population:** Head Injury*; Severe Group*: Mean Age=38.0yr. *Mild Group*: Mean Age=29.3yr. Gender: Not Reported. **Treatment:** Patients with severe injuries were divided into two groups: phenobarbital (n=50; 10 – 25 µg/ml) or control (n=76) starting at 4wk post injury for 2yr, tapering off at 3yr. Follow-up continued for 5yr. Participants with mild head injury were in a third group (n=65). **Outcome Measure:** Occurrence of seizures.	1. At follow-up, 16 (12.7%) participants with severe head injury developed epileptic attacks; eight (16%) in the treatment group and eight (10.5%) controls. **Results of mild head injury group not reported here*
Murri et al. (1992) Italy Post-test $NI_{initial}$=390 NF_{inal}= 293	**Population:** Head trauma; Gender: Male= 222; Female=71. 390 participants were treated with phenobarbital (PB) for 12 months. Only 293 participants completed the study (Male=222, Female=71). **Intervention:** Intramuscular dose of 2.5-3 mg/kg body weight per day was administered within 24 hours after trauma and PB was taken orally over a period of 12 months. **Outcome Measures:** Incidence of post-traumatic epilepsy.	1. 293 participants were treated with PB for 12 months and only 6 (2.04%) had one or more epileptic seizures. 2. One third of the participants (106) had PB levels below 15 ug/ml (12.3±2.3), while levels in the remaining two thirds (187 patients) were above this limit (19.5±4.1). Even low doses of PB may have a prophylactic action. 3. No significant differences were found between participants who completed the study and those lost to follow-up. Plasma PB levels showed no significant variation between the two groups.
Phenobarbital and Phenytoin		
Servit & Musil (1981) Czechoslovakia Cohort N=167	**Population:** TBI; Mean Age=30.6yr; Gender: Male=128, Female=39. **Treatment:** Participants in the treatment group (n=143) were administered phenytoin (160-240mg/d) and phenobarbital (20-60mg/d). The control group (n=24) was treated with conventional methods for 2yr. **Outcome Measure:** Occurrence of late seizures.	1. Post-traumatic epilepsy occurred in 25% of controls and 2.1% of the treatment group ($p<0.001$).

Discussion

The use of phenobarbital was examined in one RCT, one post-test study and one cohort study. In the RCT, Manaka (1992) found LPTS occurred at similar rates in both the treatment and control groups. In the post-test study, Murri et al. (1992) found that the administration of phenobarbital during the first 12 months post injury may have a prophylactic effect on the development of post-traumatic epilepsy. Similarly, in a cohort study, Servít and Musil (1981) reported that low doses of phenobarbital and phenytoin resulted in decreased occurrence of LPTS when compared to no prophylactic treatment.

Conclusions

There is level 2 evidence (Manaka et al., 1992) that prophylaxis with phenobarbital alone may not reduce the occurrence of late post-traumatic epilepsy among individuals with severe TBI.

There is level 2 evidence (Servit & Musil, 1981) that prophylaxis with phenobarbital in combination with phenytoin may reduce the occurrence of late post traumatic seizures.

There is level 4 evidence (Murri et al., 1992) that therapy with phenobarbital during the first 12 months post injury may have a prophylactic effect on PTE.

KEY POINTS

- Phenobarbital alone may not be effective in preventing late post-traumatic seizures.
- Phenobarbital combined with phenytoin may reduce the occurrence of late post-traumatic seizures.

Multiple Medications

Several studies examined the use of multiple medications for the prophylaxis of post-traumatic seizures. The majority of the studies examined the use of multiple anticonvulsants (e.g., phenytoin, valproate, carbamazepine), while others included other drug classes, such as barbiturates (e.g., phenobarbital).

TABLE 13| Multiple Medications For the Prophylaxis of Post-Traumatic Seizure

Author, Year Country Study Design Sample Size	Methods	Outcome
Pingue et al. (2021) Italy Case series N=341	**Population:** TBI; Gender: Male=266, Female= 75; Age: ≤65=196, >65=145; Severity: Mild=32, Moderate=60, Severe=178. **Intervention:** Participants were prescribed anti-seizure medications (ASM) as prophylactic upon arrival or as treatment. **Outcome Measures:** GCS, FIM, seizure occurrence.	1. PTS was documented in 19.4% of participants: early PTS (EPTS) in 7.0%; late PTS (LPTS) in 9.4%; both types in 3.0%. 2. Participants treated with ASM had a significantly lower risk of developing EPTS (p=0.03) but not a significantly lower risk of developing LPTS. 3. Participants who developed EPTS had an increased risk of developing LPTS, (p=0.003). 4. Participants with LPTS had a significantly higher risk of worse neurological (p<0.0001) and functional (p<0.05) outcomes than those with EPTS. 5. There was no significant difference in prevalence of mortality between the three classes of TBI severity.

Author, Year Country Study Design Sample Size	Methods	Outcome
Kancharla et al. (2019) India PCT N=79	**Population:** TBI; Age: 18-20yr=7, 21-30yrs=23, 31-40yr=22, 41-50yr=19, 51-60yr=5, >60yr; Gender: Male=54, Female=23. **Treatment:** Patients were treated with either 100mg of phenytoin (n=30), 500mg of levetiracetam (n=24) or 100mg of sodium valproate (n=25) to prevent posttraumatic seizures. **Outcome Measures:** Occurrence of seizures; immediate onset (within 24hrs of drug administration), early onset (within 7 days), late onset (>7 days)	1. Two patients (7%) on phenytoin (n=30) experienced early onset seizures, nine (30%) experienced late onset, and no seizure was seen in 19 (63%). 2. Four patients (17%) on levetiracetam (n=24) experienced early onset seizures, six (25%) experiences late onset, and no seizure was seen in 14 (58%). 3. Five patients (28%) on sodium valproate (n=25) experienced early onset seizures, seven (36%) experienced late onset, and no seizure was seen in four (16%).
Yeap et al. (2018) Taiwan Cohort N=583	**Population:** TBI; Participants without seizures before cranioplasty (n=336); 65.5% with TBI (n=220) Participants with new onset seizures (n=89): Mean age = 44.7 ± 17.5, Gender: Male=60, Female=29 Participants with no seizures (n=247): Mean age = 44.6 ± 18.4; Gender: Male=164, Female=83 **Intervention:** Prophylactic AEDs (phenytoin, sodium valproate, levetiracetam) administered for 1 week after cranioplasty. **Outcome Measures:** Occurrence of early seizures.	1. 56 participants received AEDs for 1 week and none of them had any early onset seizures (p=0.012). 2. The prophylactic use of AEDs was associated with a reduction in early seizures occurrence.
Kale et al. (2018) Turkey Cohort N=282	**Population:** Patients undergoing craniotomy for intra- (n=95) or extra-axial (n=56) brain tumours or traumatic (n=86) and non-traumatic (n=45) brain injury; Median Age=46.7; Gender: Male=148, Female=134. **Treatment:** Retrospective review of patients who received prophylactic antiepileptic drugs (AEDs) prior to craniotomy. Patients were either administered phenytoin (n=212), valproate (n=10), carbamazepine (n=18), or levetiracetam (n=42). **Outcome Measures:** Occurrence of postoperative seizures, time to seizure	1. 50 of the 282 patients experienced a postoperative seizure (17.7%). 2. The median time from surgery to seizures was 120 days. 3. Of the patients with traumatic and non-traumatic brain injury (n=131), 14 of the 20 seizures (70%) occurred within the first 7 days after craniotomy.
Sapina & Ratkovic (2017) Croatia Cohort N=226	**Population**: Post-Traumatic Epilepsy (PTE) Group (n=113): Gender: Males=67, Females=46. Complex Partial Seizures, Control Group (n=113): Gender: Males=20, Females=93. **Treatment:** Patients were either administered conventional anti-epileptic drugs (AEDs) (phenytoin, phenobarbital, carbamazepine) or new generation AEDs (topiramate, gabapentin, levetiracetam). **Outcome Measure:** Severity of EEG changes, time to remission of seizures.	1. Both groups significantly reduced the severity of EEG changes with treatment over a five-year period regardless of drug (p<0.05); there were no differences based on type of AED used. 2. In the PTE group, remission was achieved faster with new generation AEDs compared to conventional AEDs (1.4-1.8 vs. 1.7-2.0 months). 3. In both patient groups, the presence of psychiatric comorbidities significantly prolonged time to remission by 3.4mo (p<0.05).

Author, Year Country Study Design Sample Size	Methods	Outcome
Formisano et al. (2007) Italy/USA Cohort N=137	**Population:** TBI; GCS<8. *Study* 1 (prospective, n=82): Mean Age=27.1yr; Gender: Male=43, Female=12; Time Post Injury=62.1d. *Study 2* (retrospective, n=55): Mean Age=25.5yr; Gender: Male=59, Female=23; Time Post Injury=55.9d. **Treatment:** Patients were studied retrospectively and prospectively to determine if AEDs (carbamazepine, phenobarbital + carbamazepine, phenobarbital, phenytoin, clonazepam) were administered and the incidence of late PTE. **Outcome Measure:** Occurrence of PTE.	1. Within study 1, 18% had late PTE; there was no significant difference in the incidence of PTE between non-treated patients and those treated with prophylactic therapy (p=0.29). 2. Within study 2, the occurrence of late PTE was significantly higher in patients treated with an AED (phenobarbital, carbamazepine, phenytoin, or combined therapy) than those not treated (39% vs 0%, p=0.004). 3. Of those treated with AEDs (n=69), 30 showed epileptic abnormalities on their EEGs.

Discussion

In a PCT study, Kancharla et al. (2019) compared the use of phenytoin, levetiracetam and valproate for the prophylaxis of post-traumatic seizures. The authors found the efficacy of phenytoin and levetiracetam were similar for the prophylaxis of early and late PTS, while the efficacy of valproate was lower.

In a cohort study, Šapina and Ratković (2017) compared standard anticonvulsants (AEDs) (phenytoin, phenobarbital, carbamazepine) with new generation anticonvulsants (topiramate, gabapentin, levetiracetam). Both groups showed a reduction in the severity of EEG changes with treatment; however, the authors found that remission was achieved more quickly with the use of new generation AEDs.

In a prospective cohort study, Formisano et al. (2007) found that there was no significant difference in the incidence of PTE between those with no prophylactic treatment and those who received prophylaxis with carbamazepine, phenobarbital and carbamazepine, phenobarbital, phenytoin, or clonazepam.

In a cohort study, Yeap et al. (2018) found that anticonvulsant use (phenytoin, valproate and levetiracetam) was associated with a reduction in the occurrence of EPTS in individuals who underwent cranioplasty post TBI.

In a cohort study, Kale et al. (2018) found the incidence of PTS in individuals who underwent craniotomy was 17.7%, with phenytoin being the most common anticonvulsant medication used (75.2%). Since the authors did not compare different groups, results from this study should be interpreted with caution.

In a case series, Pingue et al. (2021) reported that the use of anti-seizure medication resulted in a significantly lower risk of developing early post-traumatic seizures. However, the authors did not specify the medication used for seizures, therefore findings of this study should be interpreted with caution.

Conclusions

There is level 2 evidence (Kancharla et al., 2019) that phenytoin and levetiracetam may have similar effectiveness for the prophylaxis of early and late post-traumatic seizures and may both be more effective than valproate.

There is level 2 evidence (Šapina and Ratković, 2017) that new generation anticonvulsants (topiramate, gabapentin, and levetiracetam) may result in faster remission of post-traumatic seizures, when compared to standard anticonvulsants (phenytoin, phenobarbital, and carbamazepine).

There is level 2 evidence (Formisano et al., 2007) that carbamazepine, phenobarbital and carbamazepine, phenobarbital, phenytoin, or clonazepam may not be effective for the prophylaxis of PTE in individuals with severe TBI.

There is level 2 evidence (Kale et al., 2018) that prophylactic anticonvulsants may not be continued beyond the first postoperative week; however, findings from this study should be interpreted with caution.

There is level 4 evidence (Pingue et al., 2021) that use of anticonvulsant medication may be effective for the prevention of early post traumatic seizures. However, further research comparing medications is needed.

KEY POINTS

- Phenytoin and levetiracetam may have similar effectiveness and may have more effectiveness that valproate for the prophylaxis of early and late post-traumatic seizures.
- Topiramate, gabapentin, levetiracetam may help achieve a faster remission of PTE, when compared to phenytoin, phenobarbital, carbamazepine.
- Carbamazepine, phenobarbital and carbamazepine, phenobarbital, phenytoin, or clonazepam may not be effective for late seizure prophylaxis post severe TBI.
- The use of antiseizure medication may result in a significant lower risk of developing early PTS; however, findings from studies that did not compared medications should be interpreted with caution.

Non-Pharmacological Interventions

Auricular Electroacupuncture

Auricular therapy involves the stimulation of a specific point in the ear, and it has been used to treat pain, anxiety and epilepsy, as well as for managing obesity and improving sleep quality (Hou et al., 2015). There is limited evidence on the use of auricular electroacupuncture for the prophylaxis of post-traumatic seizures.

TABLE 14 | Auricular Electroacupuncture for the Prophylaxis of Post-Traumatic Seizures

Author Year Country Study Design Sample Size	Methods	Outcome
Shen & Jiang, (2019) China Cohort $N_{Initial}$=89, N_{Final}=89	**Population:** TBI=89; *Intervention Group (Auricular electroacupuncture; n=30):* Mean Age=43.37±13.69yr; Gender: Male=25, Female=5; Time Post-Injury=Not Reported; Severity: Mild=0, Moderate=0, Severe=30. *Control Group (n=59):* Mean Age=46.63±11.73yr; Gender: Male=44, Female=15; Time Post-Injury=Not Reported; Severity: Mild=0, Moderate=0, Severe=59. **Treatment:** Retrospective study of auricular electroacupuncture (1Hz, 1/d for 30min) with or without sodium valproate (100mg orally 3/d; maximum dose 200-400mg) or edaravone (30mg edaravone + 0.9% sodium chloride, 100ml intravenous infusion, 2/d for 14d) versus control (no intervention) for the prevention of late post-traumatic epilepsy (PTE) in individuals with severe TBI. **Outcome Measures:** Incidence of late PTE.	1. Auricular electroacupuncture significantly reduced the incidence of late PTE compared to the control group (p<.01). 2. The incidence of late PTE was significantly reduced in individuals treated with auricular electroacupuncture, regardless of the concurrent use of sodium valproate or edaravone (p<.05).

Discussion

In a cohort study, Shen and Jiang (2019) compared the effect of auricular electroacupuncture with and without sodium valproate or edaravone, on the incidence of late post-traumatic epilepsy among persons with severe TBI. The authors found that auricular electroacupuncture significantly reduced the incidence of late PTE in individuals with severe TBI, regardless of the concurrent use of pharmacological prophylaxis. This intervention may appeal to individuals who experience adverse effects from pharmacological agents. Although these results are promising, future research will be required to examine the long-term efficacy of this intervention. Furthermore, it is important to note that time post-injury was not reported in this study, which limits the generalizability of the results.

Conclusions

There is level 2 evidence (Shen & Jiang, 2019) that auricular electroacupuncture may reduce the incidence of late post-traumatic epilepsy in individuals with severe TBI.

KEY POINTS

- Auricular electroacupuncture may be effective for the prophylaxis of post-traumatic epilepsy following severe TBI. However, more research is needed.

MANAGEMENT OF POST-TRAUMATIC SEIZURES

Pharmacological Interventions

Anticonvulsants

Carbamazepine

Carbamazepine is an anticonvulsant drug that is often used for the treatment of seizure disorders and conditions such as neuropathic pain and bipolar disorder (Alrashood, 2016). There is limited evidence on the use of carbamazepine for the management of post-traumatic seizures in individuals with brain injuries.

TABLE 15 | Carbamazepine for the Management of Post-Traumatic Seizures

Author, Year Country Study Design Sample Size	Methods	Outcome
Wroblewski et al. (1989) USA Pre-Post N=27	**Population:** TBI; Mean Age=24yr; Gender: Male=22, Female=5. **Treatment:** Participants taking phenytoin or phenobarbital had these medications stopped and replaced with carbamazepine. Participants were on the medication due to previous seizures (n=13) or because they were considered high risk for seizures (n=14). **Outcome Measure:** Occurrence of seizures.	1. Overall, there was a decrease in the average number of documented seizures following carbamazepine substitution. 2. For all participants after the medication switch: 10 had a decrease in seizure frequency, 13 had no change, and 4 reported an increase. 3. For the subgroup of participants with previously documented seizures before the medication switch (n=13): 10 had a decrease in seizure frequency, 1 had no change, and 2 had an increase. 4. No participants required discontinuation of carbamazepine due to toxicities.

Discussion

In a pre-post study, Wroblewski et al. (1989) examined the effects of withdrawing phenytoin, phenobarbital and primidone, and administrating carbamazepine as the sole anticonvulsant medication in a population with TBI. The authors found that substitution with carbamazepine resulted in a decrease in the average number of documented seizures (Wroblewski et al., 1989).

Conclusions

There is level 4 evidence (Wroblewski et al., 1989) that switching from phenytoin or phenobarbital to carbamazepine may be associated with a reduced seizure frequency among individuals with previous post traumatic seizures.

KEY POINTS

- Replacing phenytoin and phenobarbital with carbamazepine may help reduce seizure frequency in individuals with PTS.

Topiramate

Topiramate is an anticonvulsant that has been used as adjunctive therapy for refractory partial-onset seizures in adults and children (Glauser, 1999). Topiramate has also been used as prophylactic treatment for migraines (Hu et al., 2021; Silberstein, 2017). There is limited evidence on topiramate for the prophylaxis of post-traumatic seizures in individuals with brain injuries.

TABLE 16| Topiramate for the Management of Post-Traumatic Seizures

Author, Year Country Study Design Sample Size	Methods	Outcome
Lu et al. (2009) China Pre-Post N=227	**Population:** Epilepsy; Low-grade brain tumour (n=54), head trauma (n=58), cerebrovascular disease (n=33), intracranial infection (n=38), hydrocephalus (n=8), parasitosis (n=14), and diabetes mellitus (n=22); Mean Age=28.0±9.4yr; Gender: Male=110, Female=117. **Treatment:** Topiramate was administered to patients twice/day as either a single-drug or add-on therapy for 8 wks. Initial dose=25mg/day with subsequent increases using 25mg/day increments at weekly intervals for 4wks. If patients became seizure free >4wks, dosage=100mg/day, if not, dosage was increased until seizure cessation or 200mg/day was reached. **Outcome Measures:** Occurrence and frequency of seizures, adverse effects	1. 157 (69.2%) patients responded to topiramate (as defined by a seizure reduction of ≥50%) and 124 (54.6%) were seizure-free. 2. 32 of 58 patients with head trauma (55.2%) responded to topiramate and 18 (31.0%) were seizure-free. 3. The incidence of adverse effects (weight loss, memory impairments, paraesthesia) was 36.1%.

Discussion

In a pre-post study, Lu et al. (2009) reported that the majority of participants responded to topiramate, either administered as single medication or as an add-on therapy; in addition, topiramate was also found to be well tolerated, with most side effects being transient and reversible.

Conclusions

There is level 4 evidence (Liu et al., 2009) that topiramate may be effective for the treatment of seizures in individuals with ABI.

KEY POINTS

- Topiramate may be well tolerated and effective for the treatment of seizures post ABI; however, more research is needed to determine its effectiveness specifically for brain injury of traumatic etiology.

Benzodiazepines

Benzodiazepines work by slowing neurotransmission and are commonly prescribed for the treatment of insomnia and anxiety (Nielsen, 2017). The four benzodiazepines that are often used in clinical anaesthesia are diazepam, lorazepam, midazolam and the antagonist flumazenil (Olkkola & Ahonen, 2008).

Midazolam

Midazolam, a benzodiazepine, has been used for the induction of anaesthesia pre-surgery and for conscious sedation (Rodolà, 2006). Midazolam has also been frequently prescribed in palliative care to treat anxiety, dyspnea, delirium, nausea, vomiting, agitation, insomnia, and seizures, among other conditions (Zaporowska-Stachowiak et al., 2019).

TABLE 17| Midazolam For the Treatment of Post-Traumatic Seizure

Author, Year Country Study Design Sample Size	Methods	Outcome
Wroblewski & Joseph (1992) USA Case Series N=10	**Population:** TBI=8, ABI=1, Other=1; Mean Age=32.9yr; Gender: Male=9, Female=1. **Treatment:** Intramuscular midazolam was administered. **Outcome Measure:** Cessation of seizures.	1. All participants experienced seizure cessation within minutes of midazolam administration. 2. The only reported side effect was slight to moderate sedation.

Discussion

There appears to be very little research to evaluate the efficacy of medications given to treat seizures after they have already occurred among individuals with ABI. Wroblewski et al. (1992a) reported on a collection of ten case studies of patients with TBI treated with intramuscular midazolam for acute seizure cessation after other benzodiazepine drugs had failed. The authors reported that in all patients seizures ceased within minutes of midazolam administration. Midazolam also prevented the onset of prolonged seizures or status epilepticus. Slight to moderate sedation was the only reported side effect.

Conclusions

There is level 4 evidence (Wroblewski et al., 1992b) that an intramuscular injection of midazolam may be effective in aborting active seizure activity.

KEY POINTS

- An intramuscular injection of midazolam may help to stop seizures in individuals with brain injuries.

Surgical Interventions

Some individuals who present with post-traumatic seizures may not respond to pharmacological treatment. Yablon and Dostrow (2001) reported on a subgroup of ABI patients who experience continued PTS despite treatment with multiple antiepileptic drugs. For this special group of patients, surgical treatment may be a viable option.

Surgical Resection

Surgical resection includes procedures such as temporal lobe resections and extratemporal resections, as well as laser interstitial thermal therapy and disconnection procedures (Ahmad et al., 2020). Lobectomy accounts for about half of the surgical procedures for epilepsy, and it includes the removal of up to 4.5 centimetres of neocortex to improve seizures (Rugg-Gunn et al., 2020). Accurate localization of the exact region responsible for the development of seizures is important but can be a challenge. This is particularly true for patients with severe ABI who frequently show multiple and bilateral sites of brain injury (Diaz-Arrastia et al., 2000).

TABLE 18 | Surgical Resection for the Management of Post-Traumatic Seizures

Author Year Country Study Design Sample Size	Methods	Outcome
Hitti et al. (2020) USA Cohort N=23	**Population:** TBI; Mean Age=38±13.5yr; Gender: Male=15, Female=8. **Treatment:** Retrospective review. Patients with post-traumatic seizures after brain injury (n=23) were either treated with surgical resection (temporal lobectomy n=14, resection of cortical focus n=2), or vagal nerve stimulation (VNS) (n=7). Three patients underwent responsive neurostimulator (RNS) implantation after they were deemed not to be candidates for resection and VNS failed to reduce seizure frequency by more than 50%. **Outcome Measures:** Postoperative Engel classification, postoperative seizure frequency	1. Of the patients treated with surgical resection (n=16), 68.8% were Engel I (free of disabling seizures), 18.8% were Engel II (rare disabling seizures), and 12.5% were Engel III (worthwhile improvement) at follow-up. 2. Patients who received VNS had an average seizure frequency reduction of 30.6% ± 25.6%. 3. Patients who received RNS system replacement only experienced a reduction in seizure frequency of 9.6% ± 13.6%.
Hakimian et al. (2012) USA Case Series N=21	**Population:** TBI; Mean Age=34.7yr; Gender: Male=12, Female=9; Time Post-Injury=12.9yr. **Treatment:** Retrospective review of individuals who had an extratemporal resection (with or without temporal lobectomy) for medically intractable epilepsy. Most individuals had both frequent complex partial and generalized tonic-clonic seizures and were unsuccessfully treated with an average of 4.15 antiepileptic drugs. **Outcome Measure:** Occurrence of seizures (mean follow-up was 7yr).	1. Six participants were seizure-free, six participants had rare seizures (≤2/yr), five had a reduction in frequency, and 4 had no benefit from the surgery. 2. Two participants had significant complications (subdural hematomas).
Marks et al. (1995) USA Case Series N=25	**Population:** Head Trauma; Gender: Male=17, Female=8. **Treatment:** Participants underwent surgical resection when seizures could be localized. **Outcome Measure:** Occurrence of seizures.	1. Prior to surgery, seizures were localized to the mesial temporal region (Group 1, n=17) and extrahippocampal neocortical area (Group 2, n=8). 2. Nine participants had their seizures successfully localized and underwent a surgical procedure. Afterwards, all were seizure free. 3. 16 participants did not have their seizures adequately localized.

Discussion

In a cohort study, Hitti et al. (2020) examined three surgical procedures for the treatment of post-traumatic epilepsy including: surgical resection (temporal lobectomy or resection of cortical focus), vagal nerve stimulation (VNS), or responsive neurostimulator (RNS). The authors found that isolated mesial temporal sclerosis treated with temporal lobectomy was associated with favourable clinical outcomes (Engel I/free of disabling seizures) in most patients; these outcomes were similar to those observed in the existing literature focusing on persons with non-traumatic epilepsy.

In a case series study, Marks et al. (1995) reported that it was possible to successfully localize the seizure focus in less than half of their participants; subsequent surgical excision of the area presumed to be the

seizure focus resulted in seizure cessation in all treated individuals. The authors found that in those participants who showed a favourable result, the brain injury lesion was specifically limited to the hippocampus or neocortex; thus, making the identification and surgical resection more accurate. This study supported surgical excision of the seizure focus as a viable treatment option for a subgroup of individuals with TBI in whom the seizure focus can be accurately identified (Marks et al., 1995).

In another case series study, Hakimian et al. (2012) retrospectively examined individuals with TBI who had an extratemporal resection for PTE. After the resection, 28% of participants were seizure free, approximately 50% had a reduction in seizure frequency, and 19% did not benefit from treatment. Overall, good to excellent outcomes were achieved and the risk of complications was found to be minimal.

Conclusions

There is level 2 evidence (Hitti et al., 2020) that post-traumatic epilepsy attributable to mesial temporal sclerosis treated with temporal lobectomy may be associated with favourable clinical outcomes in the majority of individuals.

There is level 4 evidence (Marks et al., 1995) that individuals in whom the seizure focus can be accurately localized may benefit from surgical resection for post-traumatic seizures.

There is level 4 evidence (Hakimian et al., 2012) that extratemporal resection with or without temporal lobectomy may be effective for controlling medically intractable post-traumatic epilepsy.

KEY POINTS

- Surgical resection may be effective in reducing seizures in certain subpopulations of individuals with brain injuries, particularly among individuals in whom the seizure focus can be accurately localized.

Responsive Neurostimulation and Vagal Nerve Stimulation

Responsive Neurostimulation (RNS) refers to a closed-loop intracranial system that provides electrical stimulation (Ahmad et al., 2020). Vagal Nerve Stimulation (VNS) involves the stimulation of the vagus nerve via a generator that is implanted surgically and delivers pulse stimulation at fixed intervals (Ahmad et al., 2020). There is limited evidence on the use of these interventions for the management of post-traumatic seizures.

TABLE 19 | RNS and VNS for the Management of Post-Traumatic Seizures

Author Year Country Study Design Sample Size	Methods	Outcome
Hitti et al. (2020) USA Cohort N=23	**Population:** TBI; Mean Age=38±13.5yr; Gender: Male=15, Female=8. **Treatment:** Retrospective review. Patients with post-traumatic seizures after brain injury (n=23) were either treated with surgical resection (temporal lobectomy n=14, resection of cortical focus n=2), or vagal nerve stimulation (VNS) (n=7). Three patients underwent responsive neurostimulator (RNS) implantation after they were deemed not to be candidates for resection and VNS failed to reduce seizure frequency by more than 50%. **Outcome Measures:** Postoperative Engel classification, postoperative seizure frequency	1. Of the patients treated with surgical resection (n=16), 68.8% were Engel I (free of disabling seizures), 18.8% were Engel II (rare disabling seizures), and 12.5% were Engel III (worthwhile improvement) at follow-up. 2. Patients who received VNS had an average seizure frequency reduction of 30.6% ± 25.6%. 3. Patients who received RNS system replacement only experienced a reduction in seizure frequency of 9.6% ± 13.6%.

Discussion

In a cohort study, Hitti et al. (2020) examined three surgical procedures for the treatment of post-traumatic epilepsy including: surgical resection (temporal lobectomy or resection of cortical focus), vagal nerve stimulation (VNS), or responsive neurostimulator (RNS). In this study, the most common reasons for VNS implantation included a diagnosis of epilepsy with localization to multiple foci, nonlesional epilepsy, or patient refusal to proceed with resection and the required monitoring. The authors found that individuals who underwent VNS had a reduction in seizure frequency of 30.6%. From the seven patients who underwent VNS, three received RNS after VNS was not successful in reducing the frequency of seizures more than 50%. The authors found that the severity of seizures was reduced in individuals who received RNS implantation; however, average reduction in seizure frequency was only 9.6%. Results from this study should be interpreted with caution given the small number of participants who received VNS and RNS implantation; in addition, while the majority of the participants had moderate to severe injuries, individuals with mild injuries were also included in the study.

Conclusions

There is level 2 evidence (Hitti et al., 2020) that vagal nerve stimulation and responsive neurostimulation may be effective in reducing seizure frequency in certain individuals with PTE; however, more research is needed.

KEY POINTS

- More research is needed to determine the role of vagal nerve stimulation and responsive neurostimulation in the treatment of post-traumatic epilepsy.

RISK OF POST-TRAUMATIC SEIZURES

This section presents studies that addressed risk of seizures in individuals receiving a particular intervention, such as pharmacological therapy or surgery.

Pharmacological Interventions

Corticosteroids

The term 'Corticosteroids' encompasses all steroid hormones. Glucocorticoids, a type of corticosteroid, have been commonly prescribed to treat many inflammatory disorders (e.g., pneumonia, chronic obstructive pulmonary disease), and as part of immunosuppression therapy (e.g., organ transplantation) (Kapugi & Cunningham, 2019).

Dexamethasone

Dexamethasone is a glucocorticoid that has been commonly used for the postoperative treatment of nausea and vomiting, as well as for the reduction of postoperative pain (Moore, 2018). Dexamethasone has an anti-inflammatory effect, and it has been prescribed for the treatment of autoimmune disorders, allergies, ocular disorders, cancer and COVID-19 (Madamsetty et al., 2022). One study examined the risk of seizure development in individuals receiving therapy with dexamethasone.

TABLE 20| Dexamethasone and the Risk of Late Post-Traumatic Seizures

Author, Year Country Study Design Sample Size	Methods	Outcome
Watson et al. (2004) USA Cohort N=404	**Population:** Severe TBI; Gender: Male=309, Female=95. **Treatment:** Participants who were administered glucocorticoid medications (<1wk post injury; n=125) were compared to those who were not (n=279). 98% of those treated were given dexamethasone. Those in the treatment group were further divided into those administered the drug within 0-1d (n=105) and 2-7d (n=20) post injury. Follow-up continued for 2yr. **Outcome Measure:** Occurrence of late seizures (defined based on order of occurrence as first or second late seizures), mortality.	1. Compared to the untreated group, those treated within 1d were significantly more likely to develop first late seizures (p=0.04); an increase of 74% in the risk of first late seizures was seen. 2. Receiving glucocorticoids ≥ 2 days after TBI was not associated with first late seizure development. 3. There was no significant association between receiving glucocorticoids within 1d (p=0.28; HR=1.41; CI 95%, 0.75-2.63) or ≥2d (p=0.54; HR0.63; 95% CI, 0.15-2.74) after TBI and second late seizures. 4. No significant differences in the number of first (p=0.10) or second late seizures (p=0.41) were found between the treated and not treated groups.

		5. There was no cumulative effect found of glucocorticoid exposure on late seizure development (p=0.63; HR=1.16; 95%CI, 0.63-2.16). 6. No difference was noted in cumulative mortality between groups (p=0.57).

Discussion

Glucocorticoids given within one day post injury may put patients with severe TBI at an increased risk of developing late seizures (Watson et al., 2004); however, there is no association between late seizures and glucocorticoids if given after the first day post injury (Watson et al., 2004).

Conclusions

There is level 2 evidence (Watson et al., 2004) that glucocorticoid administration within 1 day post injury may put persons with severe TBI at a higher risk of late seizure development.

KEY POINTS

- Dexamethasone may increase the risk of late seizures when administered within one day post TBI.

Stimulants

Stimulants are frequently used for the treatment of attention-deficit hyperactivity disorder (ADHD), and include formulations such as amphetamine (AMP) and methylphenidate (MPH) (Steingard et al., 2019).

Methylphenidate

Methylphenidate is a stimulant that has been prescribed for the treatment of ADHD (Kimko et al., 1999), as well as to treat cognitive impairment due to older age and Parkinson's disease (Kapur, 2020). There is limited evidence on the use of methylphenidate for the prophylaxis of post-traumatic seizures.

TABLE 21| Methylphenidate and the Risk of Late Post-Traumatic Seizures

Author, Year Country Study Design Sample Size	Methods	Outcome
Wroblewski et al. (1992b) USA Case Series N=30	**Population:** TBI=25, ABI=5; Mean Age=32y; Mean Time Post Injury=14.1mo. **Treatment:** Chart review of individuals with late post-traumatic seizures treated with Methylphenidate. Majority (n=28) also received	1. Four participants had a higher seizure frequency while taking methylphenidate, 13 had a lower frequency of seizures on the medication, and 13 had no change between being on or off the medication.

	an anticonvulsant (carbamazepine or valproic acid). **Outcome Measure:** Occurrence of seizures.	2. Twenty participants had no seizures while taking methylphenidate. 3. There was a trend toward a lesser frequency of seizures in participants during methylphenidate treatment (p=0.063).

Discussion

In a case series by Wroblewski et al. (1992b), there was a trend towards decrease in seizure frequency in individuals treated with methylphenidate. However, it should be noted that anticonvulsants, carbamazepine or valproic acid were administered to the majority of patients.

Conclusions

There is level 4 evidence (Wroblewski et al., 1992a) that methylphenidate does not increase the risk of seizures among individuals with late PTS.

KEY POINTS

- Methylphenidate does not appear to increase seizure frequency among individuals with late PTS.

Surgical Interventions

Craniotomy and Craniectomy

Craniectomy refers to a surgical procedure, usually completed emergently, in which a bone flap from the skull is removed for decompression of intracranial contents (Chughtai et al., 2019). Decompressive craniectomy has been often used to treat elevated intracranial pressure in conditions such as middle cerebral artery infraction, subarachnoid hemorrhage and traumatic brain injury (Schirmer et al., 2008). Craniotomy is a surgical procedure in which a bone flap is removed from the skull temporarily to access intracranial contents; in this procedure, as opposed to a craniectomy, the bone flap is returned to the skull intraoperatively (Chughtai et al., 2019).

TABLE 22 | Craniotomy and Craniectomy as Risk Factors for Post-Traumatic Seizures

Author Year Country Study Design Sample Size	Methods	Outcome
Won et al. (2017) Germany Cohort N=139	**Population:** Acute Subdural Hematoma: Mean Age=72.7yr; Gender: Male=94, Female=45; GCS: ≤8=73, >8=66. **Treatment:** Participants either received a craniotomy or a craniectomy. **Outcome Measure:** Risk factors for seizure incidence, seizure frequency, functional outcome at 3mo.	1. 53 participants (38%) experienced seizures (40% pre-operatively, 64% post-operatively, 4% both). 2. Post-operatively, 90% of those with pre-operative seizures were seizure free for 3 mo. 3. GCS ≤8 at admission (OR 3.2), GCS ≤8 24hr post-op (OR 3.4), SDH width >1.4cm (OR 2.2) and previous treatment with anticoagulants (OR 2.4) were all independently associated with the occurrence of seizures. Surgical treatment via operation (OR 2.5) was an additional risk factor identified for post-operative seizures. 4. There was no significant difference in terms of seizure frequency between those who received a craniotomy compared to a craniectomy (p=0.06). 5. There was no significant difference in functional outcome at 3 mo between those who received craniotomy or craniectomy. 6. Those with seizures had a significantly higher risk of an unfavourable outcome compared to those without seizures at 3mo.
Ramakrishnan et al. (2015) Cohort United States N=153	**Population:** TBI; Standard Craniotomy Group: Participants (n=52); Gender: Male=80.8 %, Female=19.2%; Mean $GCS_{initial}$= 11.67, Mean GCS_{final}=13.74 Decompressive Craniectomy Group: Participants (n=33); Gender: Male=81.8 %, Female=18%; Mean $GCS_{initial}$= 6.76, Mean GCS_{final}=8.24 **Intervention:** Chart review of follow-up procedure notes of craniotomy and craniectomy participants was conducted to determine the occurrence of seizures, day of seizure onset, AED used and 30-day outcome. **Outcome Measures:** Incidence of seizures post neurosurgery.	1. Seizure rates did not significantly differ between craniotomy participants (13.5% 30-day seizure rate) and craniectomy participants (30-day seizure rate 21.2%; p = 0.35). 2. Mean time to seizure onset did not differ significantly by postoperative day between the two groups: 5.86 days in the craniotomy cohort and 8.14 days in the craniectomy cohort (p = 0.642). 3. No significant difference was identified in the frequency of AEDs used in the two groups. 4. The mean duration of hospital stay was not statistically significant between the two groups. Craniotomy participants were discharged on postoperative day 14.52 (mean) and craniectomy patients were discharged on postoperative day 15.73 (p = 0.702).
Huang et al. (2015) Taiwan Case Series	**Population:** TBI patients undergoing decompressive craniectomy (DC); Mean Age=45.5±20.4yr; Gender: Male=139, Female= 56; 3≤GCS≤5=66; 6≤GCS≤8=87; 9≤GCS≤15=42.	1. 21 of the 195 patients (10.8%) experienced an acute post-craniectomy seizure with a mean time interval between seizure and DC of 2.6±1.5 days.

Author Year Country Study Design Sample Size	Methods	Outcome
N=195	**Treatment:** Retrospective review of patients who received DC for TBI. **Outcome Measures:** Occurrence of acute post-craniectomy seizures (≥7 days of DC), Glasgow Outcome Scale (GOS) and Glasgow Coma Scale (GCS) at discharge	2. 16 of the 21 patients (76.2%) who had acute seizures developed epilepsy during hospitalization. 3. Patients with and without seizures did not differ in neurological outcome at discharge (p=0.917).

Discussion

In a cohort study, Won et al. (2017) retrospectively compared craniotomy and craniectomy among individuals with subdural hematoma in terms of subsequent seizure incidence, frequency, and functional outcomes. The authors found that there were no significant differences between the groups who received craniectomy or craniotomy in terms of the incidence of seizures. In another cohort study, Ramakrishnan et al. (2015) retrospectively analyzed patients who underwent decompressive craniectomy or standard craniotomy; while there was a trend toward increasing incidence of seizures in the craniectomy group, this finding was not significant. In a case series study, Huang et al. (2015) found that the rate of post-craniectomy seizure was 10.8%, with more than 90% of seizure attacks occurring within the first three days post craniectomy.

Conclusions

There is level 2 evidence (Won et al., 2017; Ramakrishnan et al., 2015) that there may be no difference in seizure occurrence among individuals who underwent craniectomy when compared to those who underwent craniotomy post TBI.

There is level 4 evidence (Huang et al., 2015) that acute post-craniectomy seizures may occur in 10.8% of patients, with most taking place within three days of the surgery.

KEY POINTS

- The incidence of seizures may not be different following craniectomy when compared to craniotomy.
- Acute post-craniectomy seizures occur in 10.8% of patients, mostly within 3 days of the procedure.

Conclusion

PTS are relatively common after ABI, however there is limited evidence to guide clinical decision making in terms of prophylaxis and treatment. This does not mean the interventions are not effective, but both conventional pharmacological agents as well as newer drugs have not yet been subjected to rigorous evaluation in this specific patient population (Fordington & Manford, 2020). While surgical interventions, in general, appear to be an option for the treatment of PTS in individuals who have failed pharmacological treatment and in whom the seizure focus can be readily localized, surgery is highly invasive and clinical evidence for efficacy has been limited. Furthermore, given that individuals with post-traumatic epilepsy may present with cognitive and psychosocial impairments that lead to social isolation (Piccenna et al., 2017), more interventions targeting quality of life and community reintegration are needed.

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