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CRITICAL REVIEW

Management of post-traumatic epilepsy: An evidence review over the last 5 years and future directions

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Summary

Post-traumatic epilepsy (PTE) is a relatively underappreciated condition that can develop as a secondary consequence following traumatic brain injury (TBI). The aim of this rapid evidence review is to provide a synthesis of existing evidence on the effectiveness of treatment interventions for the prevention of PTE in people who have suffered a moderate/severe TBI to increase awareness and understanding among consumers. Electronic medical databases (n = 5) and gray literature published between January 2010 and April 2015 were searched for studies on the management of PTE. Twenty-two eligible studies were identified that met the inclusion criteria. No evidence was found for the effectiveness of any *pharmacological* treatments in the prevention or treatment of symptomatic seizures in adults with PTE. However, limited high-level evidence for the effectiveness of the antiepileptic drug levetiracetam was identified for PTE in children. Low-level evidence was identified for *nonpharmacological* interventions in significantly reducing seizures in patients with PTE, but only in a minority of cases, requiring further high-level studies to confirm the results. This review provides an opportunity for researchers and health service professionals to better understand the underlying pathophysiology of PTE to develop novel, more effective therapeutic targets and to improve the quality of life of people with this condition.

KEY WORDS: **Traumatic brain injury, Epilepsy, Late seizures, Management, Community.**

Post-traumatic epilepsy (PTE) is a serious and disabling delayed consequence of a traumatic brain injury (TBI). PTE is one of the most common types of acquired (or secondary) epilepsies, which are due to a brain insult, such as trauma, tumors, stroke, and infections, and accounts for 20% of acquired epilepsy in the general population.[1,2] People with PTE commonly experience a latent or silent period of at least 6 months, and sometimes up to 20 years, between the causative injury and the onset of seizures; this provides a potential time window for intervention (Fig. 1). Because of this latency, it is essential that there is an understanding of the associated risk factors, the person's natural history, and clinical heterogeneity for appropriate treatment to be provided at the right time.

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Incidence and risk factors

PTE has been described as a particularly heterogeneous condition, specifically because of the heterogeneity associated with TBI. The types of seizures experienced by people with PTE are focal onset seizures with or without secondary generalization to bilateral tonic-clonic convulsive activity, and some people experience focal nonconvulsive seizures only.[1] Early seizures are often of the generalized tonic-clonic convulsive type in comparison to late seizures, which are mostly nonconvulsive in nature.

It is well established that the incidence of PTE increases with the severity of TBI. For example, an analysis by

Key Points

- There is no evidence for the effectiveness of pharmacological treatments in the prevention or treatment of symptomatic seizures in adults with PTE
- Limited high-level evidence for the effectiveness of levetiracetam was identified for children with PTE
- Promising low-level evidence was shown for the use of a psychoeducational intervention in assisting the management of PTE to improve quality of life
- More effective therapeutic targets are necessary for the management of PTE

Herman[3] of the relative risk (RR) for unproved seizures reported that severe TBI confers a RR 29 times that of the general population, and for mild and moderate TBI it was 1.5 and 4, respectively. It has been found that the risk of PTE is the highest within the first 2 years of TBI.[4] However, the risk of developing PTE is still high for more than 10 years later in people with moderate TBI and more than 20 years later in people with severe TBI.[5] Hence, it is not unusual for cases of PTE to occur 30–35 years after TBI, and it is important that people with TBI who live in the community undergo "vigilant long-term neurologic follow-ups."[6]

Over the last decade, numerous hospital- (mostly) and population-based studies have identified the incidence of PTE (Table 1).[7–17] Four studies of PTE in children only (three from the U.S.A.) show incidence rates ranging from 11% to 19%; three studies in adults only show varying incidence rates; and four studies involving adults and children with PTE with two studies from China report similar rates (5% and 9%). "Adults" refers to people aged 18 years and older.

Several risk factors have also been studied and documented for PTE, including the following:

1 *Personal factors*—young age or increasing age from 15 years, family history, depression, and premorbid alcohol abuse[18]
2 *Injury factors*—markers of increasing injury severity such as penetrating injuries and depressed skull fracture, seizures occurring within the first week following TBI (early seizures)[18]

Another risk factor that has recently been identified is the disruption of the blood-brain barrier (BBB), which has been observed as significant electroencephalography (EEG) slowing in the region of BBB breakdown.[19] There is some controversy as to whether early seizures increase the risk of developing PTE. Annegers et al.[5] have reported that early seizures are not an independent risk factor for late seizures. However, there is stronger evidence for a high risk of seizure recurrence subsequent to the first late seizure: 47% within a month after TBI, and 86% after 2 years following TBI.[20]

Recently, it has been identified that people with a history of depression, epilepsy, or who experience three or more chronic medical conditions at discharge are at high risk of developing PTE.[11] Also, genetic polymorphisms have been reported to increase a person's susceptibility to developing PTE, including variability in the glutamic acid decarboxylase (*GAD*) 1 gene[21] and the C677T variant in the methylenetetrahydrofolate reductase (MTHFR) enzyme.[22] A recent study has found an association with genetic variants in the gene for the inflammatory cytokine IL-1β.[23] However, further studies are needed to confirm these findings.

Pathophysiology

The pathogenic mechanisms underlying PTE are still poorly understood. However, what is known is that the pathophysiology following TBI differs depending on the

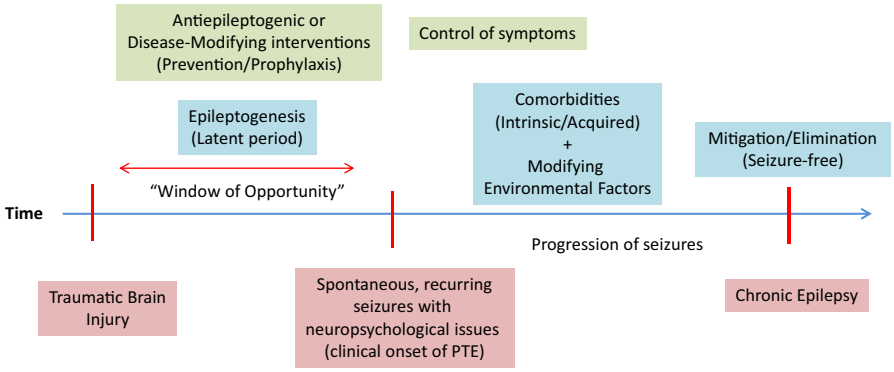

Figure 1.
Major events following post-traumatic epilepsy (PTE) over time. Figure summarizes the major events (red shaded boxes) that occur over time following TBI with the potential development of PTE and its establishment into a chronic condition. With time there are also key periods (blue shaded boxes) that contribute to the major events (red shaded boxes), including epileptogenesis that is known as the "window of opportunity" in which antiepileptogenic or disease-modifying interventions are prescribed (green shaded boxes). Once PTE has developed, management focuses on controlling the symptoms (green shaded boxes). Although, the intended goal in management is to work toward eliminating seizures so the person will be seizure-free, this is yet to be achieved in research and clinical practice.

Table 1. Overview of studies of the incidence and/or risk factors in people with post-traumatic epilepsy (PTE) over the last 5 years

Study/Design/Country	No. of people/mean age	Incidence rate or relative risk (RR)	Risk factors
Children			
Park and Chugani (2015)[1] Retrospective chart review (hospital) U.S.A.	N = 321 children with severe TBI Mean age—NR (range: 0–15 years)	47 (15%) were diagnosed with PTE "Nine (23%) of the 39 patients had the first seizure within 24 h after TBI, three (8%) patients had the first seizure between 1 day and 1 week of TBI, and 15 (38%) had a first seizure > 8 days after the injury"	N/A
Arndt et al. (2013)[2] Prospective in-hospital U.S.A.	n = 87 children with TBI Mean age 6.2 years (range: 1 month–18 years)	Seizures of any type occurred in 43.7% (37/87) Subclinical seizures were detected in 16.1% (14/87) of all patients studied	Younger age ($p < 0.001$) and increased hospital length of stay
Arango et al. (2012)[3] Retrospective chart review (hospital) U.S.A.	n = 130 children with severe TBI Mean age 7.2 years (range: 0–17 years)	19% 22 people experienced PTE (16.9%) Abnormal EEG findings were observed in 19 (14.6%) subjects, and these findings were described as: status epilepticus in 1 (5.3%), seizure activity in 11 (57.9%), and epileptiform discharges in 7 (36.8%) out of the 19 patients	"Presence of early PTE and the development of late posttraumatic seizures was evidenced ($p = 0.001$; 95% CI = 2.2, 16.5). . .. Nonaccidental trauma and young age were identified as independent predictors for the development of seizures"
Emanuelson and Uvebrant (2009)[4] Population-based retrospective follow-up (after 10 years) Sweden	109 children with TBI Mean age—NR (range: 0–17 years)	11.0% (n = 12), 9/12 (75%) had onset within the first year after injury RR 9.02 ($p = 0.0003$, 95% CI = 3.69, 22.05)	N/A
Adults			
Yeh et al. (2013)[5] Retrospective population-based cohort study (5–8 years follow-up) Taiwan and China	19,336 people with TBI and 540,322 people without TBI aged ≥15 years Mean age 39.1 years	"Adjusted HRs of developing epilepsy among TBI patients with skull fracture, severe or mild brain injury were 10.6 (95% CI = 7.14, 15.8), 5.05 (95% CI = 4.40, 5.79) and 3.02 (95% CI = 2.42, 3.77), respectively" "The risk of post-TBI epilepsy was highest within the first year after TBI (HR 38.2, 95% CI = 21.7, 67.0)"	Gender and injury—"During follow-up, men exhibited higher risks of post-TBI epilepsy Patients who had mixed types of cerebral haemorrhage were at the highest risk of epilepsy compared with the non-TBI cohort (HR 7.83, 95% CI = 4.69, 13.0)"
Kazemi et al. (2012)[6] Retrospective chart review (hospital) Iran	n = 163 veterans of war with blunt or penetrating TBI Mean age 42 years	"78% and 22% of patients with penetrating trauma experienced their first seizure during the first year and 1 year after the trauma, respectively. Only 38% of patients with blunt trauma and epilepsy, however, reported their first seizure during the first year of the trauma. The seizure frequency was significantly higher in epileptic patients with penetrating trauma ($p = 0.02$). In addition, the duration of unconsciousness was significantly longer in patients with penetrating head trauma ($p = 0.01$)"	N/A
Ferguson et al. (2010)[7] Population-based retrospective follow-up (after 3 years) U.S.A.	n = 2,118 adults (>15 years) with TBI Mean age—NR	Cumulative rate—4.4 per 100 persons for mild TBI, 7.6 for moderate, and 13.6 for severe	Severe TBI, posttraumatic seizures prior to discharge, a history of depression and people who experience three or more chronic medical conditions at discharge

Continued

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Table 1. Continued.

Study/Design/Country	No. of people/mean age	Incidence rate or relative risk (RR)	Risk factors
Adults and children			
Wang et al. (2013)[8] Retrospective chart review (hospital) China	n = 3,093 adults and children Mean age 36.69 ± 18.90 (range: 1 month–95 years)	302 (9.8%) developed PTE "6 months after discharge, 181 (59.9%) patients were identified as having PTS, and the number of PTS patients increased to 236 (78.1%) and 302 after 1 and 2 years follow-up, respectively"	"Patients who had frontal–temporal lobar contusion and linear fracture had 2.045 and 2.966 times more risk to develop PTS compared to those who did not have, respectively. Severity of injury, as measured by GCS score, also correlates with the occurrence of PTS. The moderate group (GCS 9–12) and severe group (GCS 3–8) of TBI patients were 2.041 and 4.103 times more at risk to have PTS compared to the mild group (GCS 13–15), respectively"
Zhao et al. (2012)[9] Retrospective follow-up (hospital) China	n = 2,826 adults and children Mean age 36.94 ± 14.62 (range: 4–79 years old)	n = 141 with PTE 24 cases (0.8%) had PTS, of which 16 (66.7%) continued to experience after the acute phase of their TBI, accounting for 5.0% of the total PTE cases. A total of 125 cases (88.7%) were diagnosed as presenting with late-stage seizures, occurring from 10 days to 3 years after TBI. 93/141 (66.0%) presented within 6 months after the TBI, 14/141 (9.9%) between 6 and 12 months, 22/141 (15.7%) between 1 and 2 years, and only 12/141 (8.5%) between 2 and 3 years after the TBI	Older age, greater severity of brain injury, abnormal neuroimaging, surgical treatment, and early-stage seizures
Thapa et al. (2010)[10] Prospective observation study (hospital) India	n = 520 adults and children with TBI Mean age 26.3 years (range: 1–89 years)	"At a median follow-up of 386 days, 59 (11.4%) patients developed PTS. Incidence of immediate, early and late onset seizure were 6.5%, 2.1% and 2.7%, respectively. In children, incidence of PTS was 18.3%"	"On multivariate analysis, the risk of PTS was 3.7 times higher in patients who had fallen from height, 4.4 times higher in associated medical problems, and 3.7 times higher in severe head injury (GCS < 9) at presentation"
Christensen et al. (2009)[11] Population-based retrospective follow-up (after 10 years) Denmark	n = 1,605,216 adults and children with mild and severe brain injury Mean age—NR	*At time of injury* Mild TBI RR 2.22 (95% CI = 2.07, 2.38) Severe TBI RR 7.40 (95% CI = 6.16, 8.89) Skull fracture RR 2.17 (95% CI = 1.73, 2.71) *3 years post-TBI*	Increasing severity of injury, women, people older than 15 years of age, history of epilepsy

Continued

Table 1. Continued.

Study/Design/Country	No. of people/mean age	Incidence rate or relative risk (RR)	Risk factors
		Mild TBI	
		RR 1.51 (95% CI = 1.24, 1.85)	Severe TBI
		RR 4.29 (95% CI = 2.04, 9.00)	Skull fracture
		RR 2.06 (95% CI = 1.37, 3.11)	

CI, confidence interval; EEG, electroencephalogram; GCS, Glasgow Coma Scale; N/A, not available; NR, not reported; PTS, posttraumatic seizures; RR, relative risk; TBI, traumatic brain injury.

type of injury. Closed head injuries result in diffuse axonal injury, edema, ischemia, and a cascade of secondary damage, including the release of toxic mediators, excitatory amino acids, and cytokines.[1,24] Nonpenetrating head injury has been described as producing focal contusions and intracranial hemorrhage; penetrating head injury results in "a cicatrix in the cortex" or scar tissue.[25]

There is evidence to suggest that the underlying pathological processes that result in PTE are multifactorial, including the release of excitotoxins, blood-barrier deterioration with vascular changes, parenchymal hemorrhage, and free radical damage.[3] Currently, in people with TBI no reliable molecular biomarkers have been identified that can predict the development of PTE or its outcome. It is clear that further understanding the pathophysiological mechanisms underlying PTE will assist greatly in identifying better therapeutic targets and clinically applicable biomarkers.

Management of post-traumatic epilepsy: Assessment/diagnosis

Diagnostic testing assists in the assessment of PTE so that appropriate treatments can be provided to people with PTE. Electroencephalography (EEG), which is usually used as a short (<1 h) recording but that can also be used for continuous video monitoring of seizures in epileptic conditions, has been found to be mostly nonspecific for people following TBI. Studies have concluded that it is not effective for predicting the development of PTE or disability outcome.[26,27] In the acute setting, computed tomography (CT) has been shown to be effective for assessment of areas of brain injury in people following moderate to severe TBI, but not for mild TBI cases.[1] Magnetic resonance imaging (MRI) has the highest sensitivity to detect structural brain changes and is the imaging modality of choice in people with PTE. It is also being used in a research context to investigate the effectiveness of treatments and outcomes in people with PTE.[6]

Current clinical practice guidelines

Several recommendations have been produced by the American Academy of Neurology for the management of epilepsy both in adults and in children. There is only one clinical practice guideline containing recommendations for seizure prophylaxis following TBI.[28]

"For adult patients with severe TBI (typically with prolonged loss of consciousness or amnesia, intracranial hematoma or brain contusion on CT scan, and/or depressed skull fracture):

Prophylactic treatment with phenytoin, beginning with an IV loading dose, should be initiated as soon as possible after injury to decrease the risk of posttraumatic seizures occurring within the first 7 days (Level A).

Prophylactic treatment with phenytoin, carbamazepine, or valproate should not routinely be used beyond the first 7 days after injury to decrease the risk of post-traumatic

seizures occurring beyond that time (Level B)" (page 14).[28]

Other recommendations relevant to the management of PTE in adults include the following:

"Adults presenting with an unprovoked first seizure should be informed that the chance for a recurrent seizure is greatest within the first 2 years after a first seizure (21–45%) (Level A).

Clinicians should also advise such patients that clinical factors associated with an increased risk of seizure recurrence include a prior brain insult such as a stroke or trauma (Level A), an EEG with epileptiform abnormalities (Level A), a significant brain-imaging abnormality (Level B), or a nocturnal seizure (Level B).

Clinicians should advise patients that, although immediate AED therapy, as compared with delay of treatment pending a second seizure, is likely to reduce the risk of a seizure recurrence in the 2 years subsequent to a first seizure (Level B), it may not improve QOL (Level C).

Clinicians should advise patients that over the longer term (3 years), immediate AED treatment is unlikely to improve the prognosis for sustained seizure remission (Level B). Patients should be advised that their risk for AED adverse effects (AEs) ranges from 7% to 31% (Level B) and that these AEs are predominantly mild and reversible" (page 1709).[29]

All of these study findings indicate that the management of PTE should be focused on providing people with an improved quality of life in conjunction with standard treatment. The aim of this rapid review is threefold:

1 To provide an overview of the effectiveness of assessment tools and treatment interventions for the prevention of PTE in people with moderate to severe TBI
2 To increase the awareness and understanding of this important delayed complication
3 To inform future research opportunities and considerations for best clinical practice

Methods

A rapid evidence review was conducted on the basis of (1) the need identified by health professionals and researchers in current practice to increase the awareness of the management of PTE, particularly with stakeholders in the area of brain injury (where it appears underrecognized as a serious consequence), and (2) to inform future research studies through coproduction by stakeholders in the epilepsy and brain injury fields. This type of review sits within a group of evidence synthesis methodologies, one of the most well-known being the systematic review, which is regarded as the gold standard.[30] However, the inherent limitations associated with producing systematic reviews, for example, 6-month to 2-year turnarounds and narrowed clinical questions, mean they are not realistic for decision makers, who can be time and resource limited. Hence, the rapid review, which provides a more "streamlined approach to synthesizing evidence" compared to that of the systematic review, has addressed this need.[30] It is noted that no meta-analysis involving formal assessment and estimation of effect sizes was performed as a result of the methodology used.

Rapid reviews aim to inform decision makers (researchers and health professionals) who are faced with problems or issues in clinical health care settings using the most up-to-date and relevant synthesized evidence within a short time frame of 8–12 weeks.[30] Currently, there is no standard definition of what rapid reviews are or the methodology used to produce them. With this in mind we aimed to employ as rigorous an approach to our methodology as possible by utilizing the eight-step method proposed by Khangura et al.[30] Step 8 (Ongoing follow-up and dialogue with knowledge users) is not discussed here due to time constraints resulting from project deadlines.

Steps 1 and 2: Needs assessment and question development and refinement

The topic was nominated to members of a research advisory council—the Victorian Neurotrauma Advisory Council—following an open consultation with health professionals, researchers, and funders in the Australian neurotrauma community. It was identified among 16 other topics as one of importance for pursuing as part of the Forum program of the National Trauma Research Institute (NTRI). The research methodology employed by the NTRI Forum program has been published,[31] and further information is available at http://www.ntriforum.org.au/ntri-forums. Following consultation with experts, the research question was developed and refined.

Step 3: Proposal development and approval

A proposal for the topic, including the research question, was provided to an expert panel for approval. Following approval, a search strategy was developed.

Step 4: Systematic literature search

A search was conducted with the following electronic databases: MEDLINE (See Appendix); All EBM; CINAHL; PsycINFO; and EMBASE. Search terms included *brain injuries and epilepsy* and *post-traumatic*. Google Scholar was also searched using the term *post-traumatic epilepsy* and variations relating to it. The first 100 results were screened because they were the most relevant. Articles were limited to English language and in the date range January 2010–April 2015.

Step 5: Screening and selection of studies

Studies were screened by two independent reviewers using the inclusion/exclusion criteria described below. Reference lists of included studies were also scanned to identify

further relevant references. The review process took approximately 4–6 weeks to complete, from April to May 2015.

Inclusion/exclusion criteria

Patient group: Adults (≥15 years old) and children/adolescents (15 years and younger) with TBI that is accidental, that is, not due to abuse such as shaken baby syndrome. The total sample of patients should include at least 50% people with TBI with PTE, defined as "a disorder characterized by recurrent late seizure episodes (>1 week post-injury) not attributable to another obvious cause in patients following TBI. Although the term *post-traumatic epilepsy* commonly has designated single or multiple seizures including early seizures (within the first week of injury), the term should be reserved for recurrent, late post-traumatic seizures (>1 week post-injury)."[18,32]

Exclusion: Neonates; infants; people with brain tumors, encephalitis, or subarachnoid or traumatic hemorrhage; people with stroke, cardiac arrest; people with epilepsy who suffer head injury due to an accident; in vivo (animal) studies; in vitro studies.

Intervention: Any type of management (pharmacological, nonpharmacological, or surgical and assessment tools).

Phase of care: Any.

Exclusion: None.

Study type:

Inclusion: Systematic reviews, evidence-based reviews, primary studies not included in systematic reviews (randomized controlled trials [RCTs], observational, pre-post studies).

Exclusion: Case series, case study, conference proceedings, literature reviews.

Steps 6 and 7: Narrative synthesis of included studies and report production

Data were extracted from the systematic reviews and evidence-based reviews using the following headings: (1) number of included studies, (2) type of intervention, and (3) conclusion/key findings and level of evidence. They were also categorized according to adult- or children-focused studies and pharmacological and nonpharmacological studies. Data were also extracted from the primary included studies using the following headings: (1) country, (2) type of injury, (3) number of participants, (4) intervention, (5) results, and (6) conclusions. A narrative synthesis was performed using the extracted data to identify the effectiveness of diverse pharmacological and nonpharmacological interventions in adults and children for PTE and is provided in the results section that follows.

Results

The search yielded 2,657 citations, and after screening of titles and abstracts, 131 relevant full-text articles were identified (Fig. 2, reported according to PRISMA guidelines).[33,34] A gray literature search was also conducted using Google Scholar but resulted in no additional relevant articles. *Gray literature* refers to "written material or information that is unpublished or not published commercially."[35] Experts in the field identified one additional relevant article. Following full-text review, a total of 22 documents were identified as follows:

Two systematic reviews[36] (protocol only)[37]
One meta-analysis[38]
Two evidence-based reviews[18,39]
Seventeen primary studies[27,40–54]

Overview of evidence from systematic reviews

Two systematic reviews (SRs)[36,37] were identified as being of the highest level of evidence.[55] However, one of these SRs was at protocol stage only and thus has no reported results; hence, it is not utilized in the current rapid review.[37] One meta-analysis and two evidence-based reviews were identified that provide the most recent, comprehensive overview of the management of PTE, and hence are utilized in the current rapid review.[30] Assessments and treatments for late seizures, which are the true definition of PTE, are discussed.

Pharmaceutical approaches

Adults with TBI

Most management approaches for PTE in people with TBI have for the most part focused on preventing early seizures (or prophylaxis), that is, from the time of injury to within 1 week from injury. This has potentially been influenced by reports that, following TBI, the occurrence of a seizure may result in additional brain damage or "secondary injury." A meta-analysis by Zafar et al.[38] compared the use of the older AED phenytoin (PHT) with the newer-generation AED levetiracetam (LEV) for seizure prophylaxis. The authors identified a total of eight studies (two RCTs and six observational studies) (Table 2).

Of these studies, two RCTs focused on late seizure incidence (at 6 months). The authors reported that, following pooling, the differences for PHT and LEV efficacies when compared were insignificant (odds ratio [OR] 0.96, 95% confidence interval [CI] = 0.24, 3.79); hence, there was no superiority of one drug over the other.[38] However, one of the studies included patients with glioma, not TBI, and the total number of patients was small for each group (PHT, 26, and LEV, 49), which should be considered when interpreting the results. The authors also reported that pooled results of the other studies for preventing occurrence of early seizures were not conclusive of any drug demonstrating superiority over the other (OR 1.12, 95% CI = 0.34, 3.64). Zafar et al.[38] concluded that LEV and PHT had equal efficacy for early and late seizure prevention in PTE. Given that only one RCT included people with TBI for late seizure

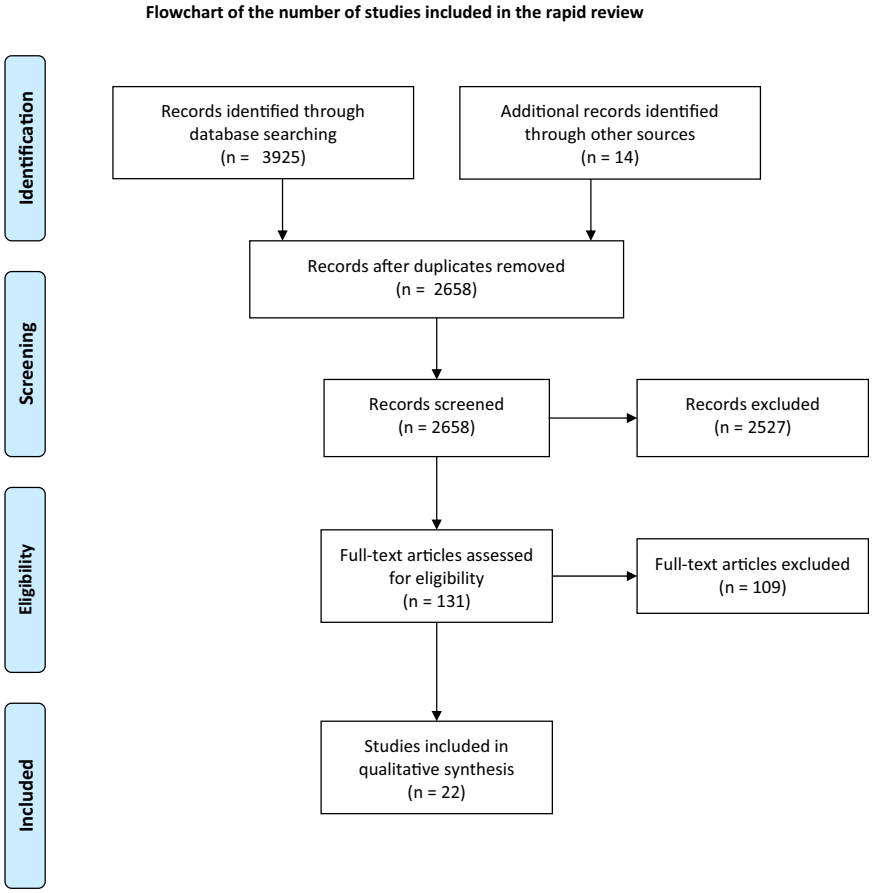

Figure 2.
Flow chart of the number of studies included in the rapid review.[34]
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prophylaxis, there is a need for further high-quality evidence to confirm these results.

An evidence-based review by Teasell et al.[18] also investigated the effectiveness of pharmacological agents in seizure prevention or prophylaxis for PTE. A total of 12 RCTs and 5 non-RCTs were identified, with the duration of treatment ranging from 6 months to 2 years (Table 2).

Phenytoin

A total of 10 RCTs investigated the efficacy of PHT for seizure prevention following PTE (Table 3). Two RCTs investigated PHT efficacy for early seizure prevention: one compared the efficacy of PHT or LEV[56] and one looked at PHT in comparison to placebo.[18,57] In both studies, no difference was observed for occurrence of early seizures following either treatment; however, people receiving LEV reported fewer side effects. In the RCT that utilized PHT and LEV, after 3 and 6 months of follow-up, people treated with LEV versus PHT performed better on the Disability Rating Scale (DRS), $p = 0.042$, and the Glasgow Outcome Scale (GOS), $p = 0.039$; however, their neurological status was worse ($p = 0.024$). Another RCT[58] did observe a reduction in seizures in the first week of PHT treatment in comparison to no effect with placebo (3.6% vs. 14.2%, $p < 0.001$), but this same effect was not observed following 1 year of treatment and at 2 years of follow-up.[18]

Late seizures

Five RCTs assessed the efficacy of PHT administration over 1 year for late seizure prevention.[18,57–61] The study by Dikmen et al.[59] reported no difference in neuropsychological performance at 1-year follow-up between PHT and placebo groups; however, from 1-year follow-up to the 2-year follow-up, the PHT group experienced negative cognitive effects. Three RCTs[58,60,62] did not observe any difference in late seizures between people who received PHT and those who received placebo for up to 2 years postinjury. Only one RCT reported a significant difference with PHT in comparison to placebo in reducing the incidence of late seizures following 1 year of treatment, 6% and 42%, respectively ($p < 0.001$).[61] However, only 91 people in total were included in the study; hence each group may have had smaller numbers only in comparison to the other studies. Further studies are warranted.

Table 2. Overview of interventions for early and late seizure prevention and treatment of post-traumatic epilepsy from evidence-based reviews

Citation	No. of included studies	Type of intervention (no. of studies)	Review conclusion (level of evidence)
Pharmacological treatments			
Adults			
Teasell et al. (2013)[1]	17 (12 RCTs, 5 non-RCTs)	Phenytoin (PHT) (7)	"Anticonvulsants provided immediately post-ABI reduce the occurrence of seizures only within the first week (*Level 1a*)
		Carbamazepine (3)	Anticonvulsants provided shortly post-ABI do not reduce long term mortality, morbidity or late seizures (*Level 1a*)
		Valproate (2)	Anticonvulsants have negative consequences on motor tasks (*Level 1b*)
		Levetiracetam (LEV) (1)	Early glucocorticoid exposure may increase seizures (*Level 2*)
		Glucocorticoids (1)	Methylphenidate may not increase the risk of seizures (*Level 4*)
		Methylphenidate (1)	Intramuscular midazolam may be effective for acute seizure cessation (*Level 5*)" (page 22)
		Midazolam (1)	
		Phenytoin or Phenobarbital or Carbamazepine or combination of all (1)	
Zafar et al. (2012)[2] Meta-analysis	8 (2 RCTs, 6 non-RCTs)	Phenytoin (PHT) (8)	"Levetiracetam and Phenytoin demonstrate equal efficacy in seizure prevention after brain injury. However, very few randomized controlled trials (RCTs) on the subject were found. Further evidence through a high quality RCT is highly recommended" (page 30)
		Levetiracetam (LEV) (8)	
Children			
Teasell et al. (2013)[1]	2 (2 RCTs)	Phenytoin (2)	"Phenytoin does not reduce early or late seizures in children post ABI (*Level 1b*)" (page 24)
Nonpharmacological interventions			
Teasell et al. (2013)[1]	1 case series (n = 25 people)	Surgical resection (1)	"Surgical excision can reduce seizures if the focus of the seizures can be localized (*Level 4*)" (page 25)

ABI, acquired brain injury; RCT, randomized controlled trial.

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Table 3. Overview of primary studies for the management of post-traumatic epilepsy

Study/Design/Country	Type of injury/no. of participants	Intervention	Results	Conclusions
Treatment—pharmacological interventions				
Bhullar et al. (2014)[41] Retrospective chart review U.S.A.	Adults with blunt severe TBI (n = 43, NP and n = 50, PP)	Phenytoin Prophylaxis (PP) versus No Prophylaxis (NP) for 7 days	"Contrary to expectation, more seizures occurred in the PP group as compared with the NP group; however, this did not reach significance (PP vs. NP, 2 [4%] vs. 1 [2.3%], p = 1). There was no significant difference in the two groups (PP vs. NP) as far as disposition are concerned, mortality caused by head injury (4 [8%] vs. 3 [7%], p = 1), discharge home (16 [32%] vs. 17 [40%], p = 0.7), and discharge to rehabilitation (30 [60%] vs. 23 [53%], p = 0.9). However, with PP, there was a significantly longer hospital stay (PP vs. NP, 36 vs. 25 days, p = 0.04) and significantly worse functional outcome at discharge based on Glasgow Outcome Scale (GOS) score (PP vs. NP, 2.9 vs. 3.4, p G 0.01) and modified Rankin Scale score (2.3 ± 1.7 vs. 3.1 ± 1.5, p = 0.02)"	"PP may not decrease early posttraumatic seizure and may suppress functional outcome after blunt TBI. These results need to be verified with randomized studies before recommending changes in clinical practice and do not apply to penetrating trauma"
Gabriel et al. (2014)[45] Single center, prospective cohort study U.S.A.	Adults (age ≥ 18) with PTE or medically intractable epilepsy (n = 19, 14 PHT and 5 LEV)	Phenytoin (PHT) or Levetiracetam (LEV) *Duration of administration was not reported	"There was no difference in the GOS-E score assessed ≥6 months after injury (5.07 ± 1.69 vs. 5.60 ± 2.07, p = 0.58). There was no difference in the secondary end points of early seizures (p = 0.53) or late seizures (p = 0.53). However, the PHT group experienced a higher rate of hospital days with recorded fever (0.20 ± 0.22 vs. 0 ± 0; p = 0.014)"	"Long-term functional outcome in patients who experienced a TBI was not affected by treatment with PHT or LEV; however, patients treated with PHT had a higher incidence of fever during hospitalization" (page 1440)
Inaba et al. (2013)[48] Prospective cohort study U.S.A.	Adults with blunt severe TBI (n = 813, 406 LEV and 407 PHT)	Phenytoin (PHT) or Levetiracetam (LEV) *Duration of administration was not reported	"There was no difference in seizure rate (1.5% vs. 1.5%, p = 0.997), adverse drug reactions (7.9% vs. 10.3%, p = 0.227), or mortality (5.4% vs. 3.7%, p = 0.236)"	"In this prospective evaluation of early PTS prophylaxis, LEV did not outperform PHT. Cost and need for serum monitoring should be considered in guiding the choice of prophylactic agent" (page 766)
Roberts et al. (2012)[54] Retrospective chart review U.S.A.	Adults with blunt or penetrating TBI who had early-onset PTE (n = 14)	With Prophylaxis (WP, levetiracetam or phenytoin) versus No Prophylaxis (NP)	"For blunt and penetrating TBI, comparing NP versus WP groups, no significant difference in seizure rate occurred regardless of GCS: GCS (3–15) (0.65% vs. 0.74%, p = 0.82), GCS (9–15) (0.73% vs. 0.69%, p = 0.94), and GCS (<8) (0.47% vs. 0.82%, p = 0.58). For just blunt TBI, comparing NP versus WP groups, again no significant difference in seizure rate occurred regardless of GCS: GCS (3–15) (0.55% vs. 0.47%, p = 0.83), GCS (9–15) (0.76% vs. 0.74%, p = 0.97),	"Significantly lower overall seizure rate was noted as compared to previously reported (0.68% vs. 4–25%). Regardless of mechanism of injury (blunt or penetrating) or severity of TBI, (GCS [3–15], GCS [9–15], or GCS [<8]) no significant difference in the

Continued

Table 3. Continued.

Study/Design/Country	Type of injury/no. of participants	Intervention	Results	Conclusions
			and GCS (<8) (0.57% vs. 0.88%, p = 0.66). For just penetrating trauma patients there were no seizures in both the NP (n = 105) versus WP (n = 42) group (p = 1)"	seizure rate was found between NP and P groups. Therefore, seizure prophylaxis may not be necessary during the early post-injury (first 7 days) period after TBI"
Pearl et al. (2013)[52] Open-label nonrandomized phase 2 trial U.S.A.	Children (age 6–17 years) with TBI and PTE (n = 45, 20 LEV and 25 placebo)	Levetiracetam (LEV) 55 mg/kg/day, twice daily, for 30 days, starting within 8 h postinjury with 2-year follow-up	"No patients died; 19 of 20 treatment patients were retained and one observation patient was lost to follow-up. The most common severe adverse events in treatment subjects were headache, fatigue, drowsiness, and irritability. There was no higher incidence of infection, mood changes, or behaviour problems among treatment subjects compared to observation subjects. Only 1 (2.5%) of 40 subjects developed posttraumatic epilepsy (defined as seizures >7 days after trauma)"	"This study demonstrates the feasibility of a pediatric posttraumatic epilepsy prevention study in an at-risk traumatic brain injury population. Levetiracetam was safe and well tolerated in this population. This study sets the stage for implementation of a prospective study to prevent posttraumatic epilepsy in an at-risk population" (page e135)
Klein et al. (2012)[50] Open-label nonrandomized phase 2 trial U.S.A.	Adults and children with TBI and PTE (n = 66 participants) LEV (46 adults and 20 children), and 60 observation group (40 adults and 20 children)	Levetiracetam (LEV) 55 mg/kg/day, twice daily, for 30 days, starting within 8 h postinjury with 2-year follow-up	"Of the 66 participants treated with levetiracetam, 2 (3%) stopped treatment owing to toxicity (somnolence). The most common adverse events were fatigue, headache, and somnolence. Mood scores and number of infections did not differ between the treatment and observation groups. Mean trough levels of levetiracetam on days 2– 30 ranged from 19.6 to 26.7 μg/ml. At 2 years, 13 of 86 adults (15.1%) and 1 of 40 children (2.5%) developed PTE. At 2 years, 5 of 46 treated adults (10.9%) and 8 of 40 untreated adults (20.0%) developed PTE (relative risk, 0.47; p = .18)"	"Treatment with 55 mg/kg/day of levetiracetam (a dose with an antiepileptogenic effect on animals) for patients with TBI at risk for PTE is safe and well tolerated, with plasma levels similar to those in animal studies. The findings support further evaluation of levetiracetam treatment for the prevention of PTE" (page 1290)
Pieracci et al. (2012)[53] Cost-minimization analysis U.S.A.	Decision tree using data from literature review with costs and charges and Monte Carlo simulation	Phenytoin (PHT) versus Levetiracetam (LEV)	"The PHT strategy was superior to the LEV strategy from both the institutional (mean cost per patient $151.24 vs. $411.85, respectively) and patient (mean charge per patient $2302.58 vs. $3498.40, respectively) perspectives. Varying both baseline adverse event probabilities and frequency of laboratory testing did not alter the superiority of the PHT strategy. LEV replaced PHT as the dominant strategy only when the cost/charge of treating	"From both institutional and patient perspectives, PHT is less expensive than LEV for routine pharmacoprophylaxis of early seizures among traumatic brain injury patients. Pending compelling efficacy data, LEV should not replace PHT as a first-line agent for this indication" (page 276)

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Table 3. Continued.

Study/Design/Country	Type of injury/no. of participants	Intervention	Results	Conclusions
			mental status deterioration was increased markedly above baseline"	
Cotton et al. (2011)[42] Cost-effectiveness analysis U.S.A.	Cost-effectiveness analysis	Phenytoin patients receive 1.0 g fosphenytoin load + 3 days of 100 mg three times a day (TID), have level drawn on day 3, "therapeutic" patients receive 100 mg TID on days 4–7, and " subtherapeutic" patients receive 200 mg TID on days 4–7; (2) levetiracetam patients receive 500 mg load + 7 days of 500 mg two times a day	"The cost of a 7-day course of fosphenytoin, phenytoin, and free phenytoin level was $37 .50, whereas the cost of a 7-day course of levetiracetam was $480.00" . . . "Quality-adjusted life years (QALY) were 23.6 for phenytoin and 23.2 for levetiracetam. As a result, the cost/effectiveness ratios were $1. 58/QALY for phenytoin and $20.72/QALY for levetiracetam. All sensitivity analyses favored phenytoin unless levetiracetam prevented 100% of seizures and cost <$400 for 7-day course"	"Phenytoin is more cost-effective than levetiracetam at all reasonable prices and at all clinically plausible reductions in post-TBI seizure potential"
Debenham et al. (2011)[43] Retrospective chart review U.S.A.	Adults with TBI (mild, moderate, and severe) and PTE (n = 1,008)	Phenytoin (PHT)—dosage and time not reported	"5.4% had early PTS, 2.3% while on prophylaxis and 3.1% while not on prophylaxis, 1.9% before reaching the hospital and 1.2% prior to phenytoin administration while in hospital. Delay of administration was 5 h. 64.8% received prophylaxis and physicians used positive CT scan as the primary decision-making parameter ($p < 0.001$). Compliance with guidelines was 99.7%. Adverse reactions occurred in 0.5%. Levels were drawn in 42.2% (52% therapeutic, 41% low, 7% high)"	"Phenytoin is used according to guidelines, with CT scan being the main decision factor for its use. The frequency of early PTS rate is low and side effects are rare. However, earlier administration of phenytoin and adequate levels could further prevent early PTS" (page 896)
Ma et al. (2010)[51] Retrospective chart review China	Adults and children with TBI and PTE (n = 159, 152 adults and 7 children)	Sodium valproate intravenously at 10–15 mg/kg/day, followed by oral valproate for 7 days	"Seven patients (4.4%) showed early posttraumatic seizures. Although the incidence was zero in patients who received sodium valproate treatment, the difference between the treatment and control groups was not statistically significant. Of the 87 severe TBI patients (GCS 3–8), 6 patients in the control group (6.9%) suffered from early seizures during the first week after TBI and no patient who received preventive therapy suffered from seizures. The difference between the treatment and the control groups was still not statistically significant. Of the 72 mild and moderate TBI patients (GCS 9–15), only 1 patient in the control	"Although the results suggest that the study is not sufficiently powerful to detect a clinically important difference in the seizure rates between the treatment and control groups, sodium valproate is effective in decreasing the risk of early posttraumatic seizures in severe TBI patients. Further prospective studies are recommended" (page 293)

Continued

Table 3. Continued.

Study/Design/Country	Type of injury/no. of participants	Intervention	Results	Conclusions
			group suffered from seizures and no patient in the treatment group suffered"	
Kazerooni and Bounthavong (2010)[49] Cost-effectiveness analysis U.S.A.	Decision analysis model	Phenytoin (PHT) versus Levetiracetam (LEV)	"The total direct costs for seizure prophylaxis were $8784.63 and $8743.78 for levetiracetam and phenytoin, respectively. The cost-effectiveness ratio of levetiracetam was $10044.91 per successful seizure prophylaxis regimen (SSPR) compared to $11525.63 per SSPR with phenytoin. The effectiveness probability (patients with no seizures and no ADR requiring change in therapy) was higher in the levetiracetam group (87.5%) versus the phenytoin group (75.9%). The incremental cost effectiveness ratio for levetiracetam versus phenytoin was $360.82 per additional SSPR gained"	"Levetiracetam has the potential to be more cost-effective than phenytoin for early onset seizure prophylaxis after neurosurgery if the payer's willingness-to-pay is greater than $360.82 per additional SSPR gained"
Nonpharmacological approaches				
Englot et al. (2012)[44] Case-control study from a VNS Therapy Patient Outcome Registry (Cyberonic, Inc.) U.S.A.	Adults with PTE (n = 2,080, 317 PTE and 1,763 non-PTE)	Vagus nerve stimulation (VNS) therapy	"After VNS therapy, patients with PTE demonstrated a greater reduction in seizure frequency (50% fewer seizures at the 3-month follow-up; 73% fewer seizures at 24 months) than patients with non-PTE (46% fewer seizures at 3 months; 57% fewer seizures at 24 months). Overall, patients with PTE had a 78% rate of clinical response to VNS therapy at 24 months (that is, ≥50% reduction in seizure frequency) as compared with a 61% response rate among patients with non-PTE (OR 1.32, 95% CI = 1.07, 1.61), leading to improved outcomes according to the Engel classification ($p < 0.0001$, Cochran-Mantel-Haenszel statistic)"	"Vagus nerve stimulation should be considered in patients with medically refractory PTE who are not good candidates for resection. A controlled prospective trial is necessary to further examine seizure outcomes as well as neuropsychological outcomes after VNS therapy in patients with intractable PTE" (page 970)
Hakimian et al. (2012)[47] Retrospective chart review U.S.A.	Adults (age ≥ 18) with PTE or medically intractable epilepsy (n = 21, 8 with mild to moderate TBI and 12 with moderate to severe TBI)	Extratemporal resection (with or without temporal lobectomy) with 1 year follow-up	"In long-term follow-up 6 patients (28%) were seizure-free and an additional 6 (28%) had a good outcome of 2 or fewer seizures per year. Another 5 patients (24%) experienced a reduction in seizures, while only 4 (19%) did not attain significant benefit. The presence of focal encephalomalacia on imaging was associated with good or excellent outcomes in 83%. In 8 patients with the combination of encephalomalacia and invasive intracranial EEG, 5 (62.5%) were found to be seizure free. Normal MRI examinations	"Many patients with extratemporal PTE can achieve good to excellent seizure control with epilepsy surgery. The risks of complications are acceptably low. Patients with focal encephalomalacia on MRI generally do well. Excellent outcomes can be achieved when extratemporal resection is guided by intracranial EEG

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Table 3. Continued.

Study/Design/Country	Type of injury/no. of participants	Intervention	Results	Conclusions
			preoperatively were associated with worse outcomes, particularly when combined with multifocal or poorly localized EEG findings. Two patients suffered complications but none were life threatening or disabling"	electrodes defining the extent of resection" (page 1)
Bellon and Rees (2009)[40] Nonrandomized controlled study Australia	16 people with PTE	Psychoeducational intervention (n = 8) composed of 2-h social and skill development workshop per week for a 6-month period vs. no treatment (n = 8)	"Results indicated improved levels of self-awareness by intervention participants, which was not sustained at 6-month follow-up. For the control group, established views and behaviours persisted over time with no improvement"	"The study indicates that a psychoeducational intervention designed for people with brain injury can improve self-awareness and understanding of PTE, and reduce social isolation, such that seizures are better managed, participation in community activities are established, and the rehabilitation process enhanced"
Assessment				
Steinbaugh et al. (2012)[27] Secondary analysis of a prospective RCT[56] U.S.A.	Adults with TBI and PTE (n = 46)	Continuous video-EEG for initial 72 h following administration of levetiracetam (LEV) or fosphenytoin (PHT)	"Severity of generalized slowing tended to be associated with outcomes in both treatment groups (discharge DRS, p = 0.042; discharge GOS-E, p = 0.026; 3 month DRS, p = 0.051). The presence of focal slowing, the presence and frequency of epileptiform discharges and the presence of seizures were not predictive of outcome in either treatment group (all p > 0.15)"	"While it has been shown that LEV is associated with better outcome than fos-PHT when used as seizure prophylaxis in brain injury, aside from severity of generalized slowing, electrographic findings of focal slowing, epileptiform discharges, and seizures were not themselves associated with outcomes in patients with TBI or SAH enrolled in a randomized clinical trial" (page 280)
Gupta et al. (2014)[46] Retrospective chart review U.S.A.	Adults with TBI or medically refractory epilepsy (n = 123) 57% had temporal lobe epilepsy (TLE), 35% had frontal lobe epilepsy (FLE), and 3% each had parietal and occipital lobe epilepsy	Continuous video-EEG over a 10-year period	"Twenty-two patients, 13 of whom had MTS, proceeded to surgical resection. At a mean follow-up of 2.5 years, Engel Class I outcomes were seen in 69% of those with TLE and 33% of those with FLE"	"Our findings suggest PTE is a heterogeneous condition, and careful evaluation with video-EEG monitoring and high resolution MRI can identify distinct syndromes. These results have implications for the design of clinical trials of antiepileptogenic therapies for PTE" (page 1439)

ADR, adverse drug reactions; CI, confidence interval; CT, computed tomography; DRS, Disability Rating Scale; EEG, electroencephalography; GCS, Glasgow Coma Scale; GOS-E, Glasgow Outcome Scale-Extended; MTS, Medial Temporal Seizures; OR, odds ratio; PTS, posttraumatic seizure; RCT, randomized controlled trial; SAH, Sub-arachnoid haemorrhage, TBI, traumatic brain injury.

Seventeen primary studies identified were not included in the meta-analysis[38] or evidence-based reviews.[18,39] Most of the studies involved adults with PTE, except for three studies—two of which involved adults and children with PTE[50,51] and one of which included children aged 6–17 years with PTE only.[52] Most of the pharmacological intervention studies focused on the prevention of early seizures in adults following TBI (Table 3).

In total, three studies utilized the AEDs—PHT and LEV—with one study being a prospective cohort study comparing the drugs to each other[48] and the other two studies utilizing either PHT or LEV in comparison to no preventive treatment.[45,54] In all studies, there were no significant differences in seizure rates between treatments. Roberts et al.[54] included adults with blunt TBI and penetrating TBI and found that people with penetrating TBI only did not experience any seizures. However, when compared to those with no preventive treatment, there was no significant difference. The authors concluded that preventive treatment with either PHT or LEV may not be necessary. Gabriel et al.[45] support these findings, further reporting that people who were treated with PHT had a higher rate of days spent in the hospital as a result of fever. Therefore, no treatment may be more cost-effective.

Klein et al.[50] conducted an open-label non-RCT (Phase II) study of LEV in comparison to placebo in adults and children with TBI. There was a trend for LEV reducing PTE at 2 years follow-up compared to placebo in both adults (15.1% vs. 10.9%) and children (20% vs. 2.5%); however, these results were not statistically significant, possibly because of the small numbers per group (Table 3). Two people discontinued the trial because of toxicity associated with LEV. There were common side effects reported, including fatigue and headache.

Two retrospective chart reviews investigated the effectiveness of PHT for the prevention of seizures in adults following TBI.[41,43] One of the studies utilized people with all types of TBI (mild, moderate, and severe);[43] the other utilized only severe TBI. In both studies there was no significant difference in the rate of seizures following PHT administration. One study reported that PHT administration was delayed by 5 h and that levels were not adequate to show any clinical change, which may have had an effect on the preventive effect of PHT.[43] Interestingly, Bhullar et al.[41] reported that although no significant difference was observed with PHT and placebo, people in the PHT group experienced more seizures. Again, like the study by Gabriel and Rowe,[45] it was found that people in the PHT group experienced more days in the hospital, which was significant in comparison to those in the placebo group; additionally, their functional outcome was significantly worse.

There was only one primary study identified for pharmacological therapy for children with PTE.[52] This open-label, non-RCT (Phase II) study investigated the effectiveness of LEV for preventing PTE. Of the 40 subjects treated for 30 days and followed up after 2 years, only one child developed PTE (Table 3). Pearl et al.[52] also reported the treatment to be well tolerated and safe. Further studies are needed to confirm these findings.

Three cost-minimization/effectiveness studies[42,49,53] investigated the pharmacological agents PHT and LEV to discern which treatment was less expensive, given that both are used for prevention of early seizures following TBI. Kazerooni and Bounthavong[49] provided the total direct costs incurred with both treatments and reported an incremental cost-effectiveness ratio in favor of LEV (vs. PHT) of $360.82 per successful seizure prophylaxis regimen. The effectiveness probability (e.g., no seizures or adverse drug reactions) was higher for LEV than PHT, 87.5% and 75.9%, respectively. In contrast, Pieracci et al.[53] found that PHT was superior to LEV from both a patient and an institutional perspective (Table 3). However, these costs were not total direct costs incurred, as Kazerooni and Bounthavong[49] reported. Another cost-effectiveness analysis by Cotton et al.[42] supported the findings of Pieracci et al.[53] that PHT is more cost-effective than LEV over a 7-day seizure prophylaxis course. Interestingly, Cotton et al.[42] studied people with mild and moderate TBI only and did not observe a significant difference between treatment and no treatment. It should be noted that people with moderate and severe TBI are at higher risk of PTE, and further prospective cost-effectiveness studies in these cases is warranted.

Carbamazepine and phenobarbital

Two RCTs were identified using carbamazepine[63] and phenobarbital,[64] and one non-RCT was identified for carbamazepine in comparison to placebo.[18,65] Both RCTs and the non-RCT reported no difference between carbamazepine and phenobarbital in comparison to placebo in seizure occurrence after 2 years of treatment.

Sodium valproate

Two RCTs compared treatment with valproate for 1 month and 6 months with placebo.[66,67] There was no difference among the groups in seizure occurrence at any time point; however, a trend of higher mortality following treatment with valproate was observed.

One retrospective study investigated intravenous sodium valproate for seizure prophylaxis in adults and children with TBI.[51] Most of the population were adults, with only 7 children included. Ma et al.[51] found that people who received sodium valproate did not experience any seizures; however, when compared to those who did not receive any treatment there was no statistically significant difference. In people who did not receive treatment, 6 people who had severe TBI and 1 person with mild to moderate TBI experienced seizures (Table 3). Because this is only one lower-quality study, further prospective studies are needed to confirm any effectiveness of sodium valproate for the treatment of PTE.

Other pharmacological agents (methylphenidate, glucocorticoids, midazolam)

Two studies investigated the efficacy of other pharmacological agents, such as methylphenidate and glucocorticoids, for seizure prophylaxis following PTE.[18,68,69] There was no difference in the occurrence of seizures following glucocorticoid treatment; however, there was an observed trend for a lower incidence of seizures with methylphenidate treatment ($p = 0.063$).

Another study utilized midazolam intramuscularly (0.5–20 mg) for the treatment of late seizures when they occurred in people with PTE.[18,70] There was a significant cessation observed following treatment, showing an effect within minutes. Treatment with midazolam also prevented prolonged seizures (or status epilepticus). This has been the only study to treat seizures acutely when they occur in people with PTE. However, there were only 10 people with PTE; therefore, further higher-quality studies are needed to confirm these results.

Children with TBI

There were only two RCTs identified for seizure prophylaxis in children with PTE using PHT.[18,71,72] One of the RCTs looked at the efficacy of PHT on late seizure occurrence and included 46 children with a penetrating or blunt TBI but did not observe any difference between the PHT and placebo groups.[72] A more recent RCT[71] utilized a larger number of children ($n = 102$) and investigated PHT treatment in comparison to placebo on early seizures (within 48 h). There was no difference in the incidence of seizures between PHT and placebo, at 7% and 5%, respectively.

Surgical approaches

Some people with seizures following PTE do not see any great improvement of their seizures or their seizures cannot be completely controlled with the use of AEDs. In these cases of drug-resistant epilepsy, surgical treatment may be considered as an option to attain seizure control and potentially reduce the amount of AEDs required. However, it should also be noted that certain issues, including bone flaps and dural adhesions, can result from surgery.

Teasell et al.[18] identified only one case series of patients with PTE who had surgical treatment.[73] The study involved 9 people who had their seizure foci identified with a variety of presurgical assessments (including MRI and EEG monitoring) and consequently underwent surgical resection. Although not specially reported in all people who underwent surgery, when the target of seizures was accurately identified and the focus removed a reduction in the occurrence of seizures was observed. In patients whose seizure focus was localized in the hippocampus and temporal neocortex, surgical resection was more successful because the area was easier to accurately identify. However, this is only one small study and requires further evidence to confirm this treatment approach as part of unresolved management. This type of approach is not applicable to all people with PTE; in many patients the seizure focus can be difficult to localize, may arise from multiple locations, or may involve brain regions responsible for key functions, such as the motor or language cortex.[6]

Two surgical intervention studies were identified for the treatment of adults with PTE.[44,47] One study was a retrospective case-control study of 317 adults with drug-resistant PTE compared with 1,763 patients with drug-resistant non-PTE who were treated with a vagal nerve stimulator (VNS) (Table 3).[44] Englot et al.[44] reported a significant reduction in seizures (of 73% at 2 years follow-up) following VNS therapy in people with PTE, which was higher than that in patients treated for non-PTE (61%). These promising findings require further higher-level studies to confirm the effectiveness of VNS specifically for PTE.

Hakimian et al.[47] conducted a retrospective review of 21 adults with PTE to investigate the effectiveness of extratemporal resective epilepsy surgery. It was found that at 1 year postsurgery most people had a reduction in seizures, with 6 people being completely seizure-free (Table 3). However, 4 people did not have any reduction in their seizures. People who had good outcomes were those in which their seizure focus was identified accurately by MRI and intracranial EEG electrodes. People who had multiple seizure foci had worse outcomes. The study involved a small sample of subjects ($n = 21$); hence, larger higher-quality studies are needed.

Bellon and Rees[40] conducted a non-RCT in 16 people with PTE to investigate the effectiveness of a psychoeducational intervention for improving psychosocial and cognitive functioning. Although the results showed an improved self-awareness and understanding of PTE and better management of seizures, the effect was not sustained at 6 months following treatment (Table 3). A higher-level study with a larger sample is needed to confirm these promising results.

Assessment/diagnosis of PTE

Two studies investigated continuous video-EEG for the assessment of PTE.[27,46] One study conducted a secondary analysis of EEG data recorded for 72 h (to detect seizure activity) in an RCT of people with PTE following treatment with PHT or LEV (Table 3).[27] There were no significant differences in focal slowing, seizures, and epileptiform discharges for either treatment. However, the severity of generalized slowing in people treated with LEV was significantly associated with better outcomes on the Disability Rating Scale and the Glasgow Outcome Scale—Extended after 3 months. Gupta et al.[46] used EEG recordings to detect changes in people with PTE over a 10-year period. Multiple syndromes were reported using EEG for monitoring and evaluation (Table 3).

In summary, studies in adults with TBI using the pharmacological interventions PHT and LEV have not unequivocally shown efficacy in reducing the occurrence of seizures. Treatment with PHT in comparison to LEV results in more days spent in the hospital as a result of adverse effects such as fever. Although it appears the PHT is less expensive than LEV for seizure prevention, further evidence is needed. There is high-level evidence for LEV being effective in the reduction of PTE in children following 2 years of follow-up; however, further studies with larger samples are needed to confirm these findings.

Sodium valproate did not show any significant effect on PTE following 7 days of prophylaxis (low-level evidence). Vagus nerve stimulation therapy significantly reduces the frequency of seizures in people with drug-resistant PTE, but further higher-level studies are needed to confirm that there is a specific benefit for this treatment approach in patients as compared to patients with drug-resistant non-PTE. In selected patients with PTE, accurate identification with MRI and EEG followed by surgical resection of focal seizures can significantly reduce the frequency of seizures. A psychoeducational intervention showed promising results for improving self-awareness and understanding of PTE and better management of seizures in people with TBI for 6 months.

Discussion

This is the first rapid evidence review to provide a summary of all the available evidence on the management and prevention of PTE. It is the intention to provide researchers, clinicians, and health service professionals a better understanding of this unappreciated but important delayed consequence of TBI. In addition, research efforts and priorities can be identified to facilitate collaboration between researchers in both epilepsy and brain injury fields. Clinicians and health professionals can use this rapid review as a basis for gaining a global perspective of assessment and treatments in PTE to assist in their practice to improve the quality of life for people experiencing PTE.

All identified studies to date have utilized pharmacological treatments on their own, revealing no clear evidence effectiveness in the prevention or symptomatic treatment of PTE in adults. Although the pathophysiology of PTE is still poorly understood, some mechanisms are implicated in its development, including alterations in DNA methylation and changes in expression of particular genes.[74] Early evidence of the complexity of the pathophysiology does suggest that there may be more than one mechanism involved.[25] It is not difficult to see that current pharmacological treatments that have targeted only one particular mechanism have been ineffective. Further investigation using multiple pharmacological treatments that target different mechanisms may achieve better efficacy. Future research efforts should focus on uncovering and identifying the pathophysiology involved so that more specifically targeted treatments can be devised.

The challenge of translation of treatments from "bench to bedside"

One of the major challenges limiting the development of improved diagnosis and treatment of PTE is that the pathophysiology is relatively unknown and understudied in humans.[11] However, the use of animal models with PTE have greatly assisted in uncovering underlying consequences that result from PTE and, hence, potential therapeutic targets. Models used for TBI include lateral fluid percussion, weight drop, and controlled cortical impact.[75] There is wide use of the lateral fluid percussion injury model in rats, but the model does not have all the clinical features of PTE observed in humans. In particular, although a latent period is seen in most animal models of epilepsy, the period is not as long as can be experienced in human PTE, that is, 2–20 years following TBI. A lack of consensus currently exists for a well-accepted animal model that is truly reflective of the mechanisms and events occurring in humans experiencing PTE.

Evidence exists for a potential genetic susceptibility to PTE; however, currently no genetic animal models investigate potential therapies for management. Three studies have found significant genetic variations in the adenosine A1 receptor,[76] methylenetetrahydrofolate reductase (MTHFR) enzyme,[22] and glutamic acid decarboxylase (GAD)[21] in humans who develop PTE. These findings may be useful in establishing therapeutic targets for the treatment of PTE and they require further investigation.

Although in animal models of PTE pharmacological interventions have been reported to prevent PTE from occurring, none has been shown to be effective in humans. The treatments studied in clinical trials were designed primarily to symptomatically control seizures (i.e., AEDs), so their mechanisms of action may be different from that associated with the development of PTE and consequently ineffective.[75] This may also be related to the time in which the treatment is administered in humans. For example, studies of valproate indicate that a continuous administration for 24 h following a seizure occurrence provides better protection in affected regions of the brain than administration before a seizure has occurred (prevention).[75] It is important that the therapeutic window is accurately identified for the treatment to have an optimal effect. Animal models need to be clinically validated, and treatments that show effectiveness in one model should reflect the same effectiveness in other models. This is particularly true in animal studies that use multiple treatments at the same time.[75] The development of PTE is generally believed to be a multifactorial process, so more than one treatment (or a combination of treatments) may prove to be more effective for the treatment of PTE.

What impact does PTE have on quality of life?

PTE can have a significant negative effect on the quality of life (QoL) of people with TBI. Following a return to the community, people with TBI have to learn to cope with and adjust to major changes in their life, including the reestablishment of their self-identity. PTE adds a complexity to the existing consequences of TBI, making reintegration into the community difficult and challenging. The fact that the onset of epilepsy occurs months or years after the TBI means that it usually occurs at a time when people are well along the road to reestablishment of their life postinjury. The development of epilepsy represents a serious setback that can affect people's independence, job opportunities, recreational pursuits, mental health, and safety.[77] The impact is exacerbated by a disconnection from the supports originally in place for the TBI, which usually have been discontinued by the time of seizure onset. Furthermore, PTE usually requires the taking of AEDs on a long-term basis, and these can have negative side effects that influence a person's QoL and neuropsychiatric symptoms.

An interesting finding from the current rapid review is the identification of a nonpharmacological psychoeducational intervention that showed effectiveness in assisting people in managing their seizures.[40] This promising intervention in conjunction with pharmacological interventions may be beneficial for some people in improving their quality of life. Psychosocial and cognitive functioning can be significantly impaired following the development of PTE, leading to social withdrawal and issues with returning to or seeking employment. Evidence in support of these effects is increasing, with three studies published within the last 5 years.[2,77,78] One study conducted a retrospective analysis of QoL in people with PTE (n = 105) 1 year after TBI. Liu et al.[78] found a significant decline in the QoL-31 Scale, the Self-Rating Depression Scale (SDS), and the Self-Rating Anxiety Scale (SAS) in people with PTE in comparison to a control group. A multiple regression analysis revealed several major factors that influenced these findings in QoL in people with PTE. These included anxiety, therapeutic compliance, depression, poor control of epileptic seizure, and the site of trauma.

Bushnik et al.[2] investigated the impacts of PTE on people with TBI after 1, 2, and 5 years. Two groups of people post-TBI were compared: those with PTE and those without PTE (n = 91).[2] A number of people in both groups reported living alone a year after their injury, and this trend continued after 5 years. People with PTE reported utilizing "more dependent forms of transportation," such as public transport or transport by another person. Significant impacts were observed in functional outcome measures such as the Disability Rating Scale, with people with PTE showing poorer results. Psychosocial outcomes were also affected, with lower scores in the Satisfaction With Life Scale for people with PTE in comparison to those without PTE.

A prospective multicenter mixed-method study investigated the impacts of PTE in people 5–13 years after TBI (n = 25).[77] Half of the participants did not return to driving and had their license suspended. Interestingly, some participants who had their driver's license reported that they still experienced seizures. Almost half of the participants reported that the occurrence of seizures affected their ability to cope with their brain injury and they felt that as a result their recovery was significantly impaired. Several people reported that the seizures prevented them from engaging in social activities as reflected by the Craig Handicap Assessment and Reporting Technique Short Form (CHART-SF), which indicates participation or handicap and on which most issues were reflected in the occupation and social integration subscales.[77]

This could suggest that a multicomponent approach may be more effective and improve the QoL of people with PTE. The paucity of nonpharmacological treatments in this area, however, requires further investigation.

The use of longitudinal studies of the lived experience of people with PTE may also facilitate the design of interventions aimed at improving QoL. Early evidence of the lived experience of PTE on QoL was illustrated in this review by three studies that revealed an effect on recovery and social participation. Unfortunately, the studies mostly looked at people with PTE at 1 or 5 years following injury, with one of the studies looking at a small number of people up to 13 years following injury. The longer-term effects of living with PTE and the effects in some people who develop PTE more than 10 years after TBI are currently unknown and require further investigation to identify supports to improve QoL.

There is also a need for diagnostic evaluation to confirm PTE if there is any question of the diagnosis, in particular in the case of psychogenic nonepileptic seizures (PNESs). PNESs are "events that resemble epileptic seizures but that are not due to paroxysmal neuronal discharges or other physiologic abnormalities and that have a presumed psychological origin" (page E65).[79] As well as being common in the general population, PNESs are common in veterans and returned military service people who may not be diagnosed until much later.[80] A retrospective analysis of veterans with a diagnosis of PNES found that over 50% had TBI or PTE in comparison to only 37% of veterans with a diagnosis of epileptic seizures. The TBI was mild for 87% of veterans with PNES, and most of them had a previous diagnosis of post-traumatic stress disorder (PTSD). This may indicate a role of PTSD in the development of PNES; this should not be ruled out during diagnostic evaluation for PTE.

Identifying biomarkers

Another issue identified is an urgent need to find biomarkers for people at risk of developing PTE. Recent evidence in an animal model of PTE used quantitative MRI biomarkers.[81–83] Immonen et al.[81] were able to predict the

development of seizures and epileptogenesis at 9 days, 23 days, 2 months, and 1 year using certain MRI biomarkers. Although this is an exciting step in predicting PTE using a widely available diagnostic technique, there are limitations of the animal model used and the findings need to be validated in clinical studies.

A dual biomarker and genetic study in adults with moderate to severe TBI investigated the development of PTE and the involvement of interleukin 1 beta (IL-1β).[84] The ratio of cerebrospinal fluid (CSF) and levels of IL-1β in serum samples were analyzed and found to vary with the development of PTE over time. This promising association is important to consider as a key target for treatment intervention because of the inflammatory damage following TBI. Therefore, further studies should confirm the role of IL-1β and associated factors in the development of PTE, in particular because of the heterogeneous nature of TBI.

Strengths and limitations of the current review

This rapid review provides a high-level synthesis of evidence on the management of PTE from the last 5 years. It finds that there is no evidence of effectiveness of pharmacological treatments for the prevention and treatment of PTE in adults and only a little high-level evidence for one pharmacological treatment—levetiracetam—in children. These findings suggest that greater collaborative efforts between researchers and health professionals should be pursued to identify novel, more effective treatments. Furthermore, an emphasis on health professional and patient organization awareness of this underappreciated condition will assist in better understanding it and developing strategies (e.g., holistic approaches) to improve the quality of life in people who experience PTE.

A major limitation of this current review is the use of a rapid review methodology that has not yet been validated or universally accepted.[30] Currently, there is also "a lack of an accepted or validated definition"[30,85]; however, this has not prevented producers of rapid reviews from publishing or disseminating their work for policy or practice change.

Because of the flexible nature of rapid reviews (varying intentions and purposes), several approaches are being used and published. Tricco et al.[86] have recently conducted an international survey (and used a modified Delphi approach) among producers of rapid reviews to investigate which approaches/methodologies are used and to explore their perceptions of the comprehensiveness, accuracy, feasibility, and risk of bias of rapid reviews. The authors report that among six different approaches identified, experts reported the most feasible approach and with the lowest perceived risk of bias was one in which the search is limited by date and language, study selection is carried out by one reviewer only, and data abstraction and quality appraisal are conducted by one reviewer and one verifier. The authors also report that the most common approach identified was updating the literature search of previous reviews.[86] This is a well-known limitation of systematic reviews that may have been published several years previously but that have not been updated with relevant evidence or that are awaiting an update by the original review authors or, when the authors are not available, by another group.

With the use of several different approaches for the production of rapid reviews, there can be an associated loss of methodological rigor and objectivity. The systematic review, or gold standard as it is known in evidence synthesis methodology, does employ methodological rigor and transparency as key strengths. It should be noted that rapid reviews have been produced as a solution to the limitations associated with systematic reviews, such as their being costly to conduct and having a long time frame for completion (6 months–2 years).[30] A key strength of rapid reviews reported by Lambert et al.[87] is their quick production time frames in conjunction with their tailored nature that addresses specific questions in policy. Polisena et al.[88] reported that rapid reviews are useful "to inform decision making with regards to funding health care technologies, services and policy, and program development."

Therefore, further investigation is needed to identify what constitutes a rapid review and what guidelines should be considered for their conduct and reporting. Recent progress has already commenced this year with the Rapid Review Summit Planning Committee, which hosted a rapid review summit in Vancouver, Canada.[89] Furthermore, a methods group known as the Cochrane Rapid Reviews Methods Group (RRMG) has just been established by two groups—the Ottawa Methods Centre based at the Ottawa Hospital Research Institute (OHRI) and the Cochrane Collaboration in Austria—to "better inform 'rapid review' methodology."[90] It is envisaged that this group will assist Cochrane groups that may want "to undertake abbreviated Cochrane reviews making them more streamlined, timely, and relevant to end-users."[90]

The American Academy of Neurology clinical practice guidelines for seizure prophylaxis in adults with severe TBI are not currently based on the findings of this rapid review. It is important that these guidelines are updated with the existing evidence so that clinicians are guided by the most effective management. The guidelines were published in 2003, more than 10 years ago. There is an urgent need for clinicians to review the existing guidelines using this rapid review.

This rapid review summarizes all assessment and treatment interventions for the management of PTE. Furthermore, it illustrates the significant effect that PTE has on the QoL of people who develop this "second"-punch consequence and the challenges we face in translating findings from "bench to bedside." Future research on the pathophysiology of PTE and biomarkers of those at high risk and collaboration among researchers in the epilepsy and brain injury fields are the keys to understanding this disease and

in making progress with such an unappreciated consequence of TBI.

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Disclosure

The authors have no conflicts of interest to declare. No competing financial interests exist. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

iAppendix

1 Brain Injuries/
2 Craniocerebral Trauma/
3 ((head* or brain*) adj2 (injur* or trauma*)).ti,ab.
4 or/1-3
5 exp Epilepsy, Post-Traumatic/
6 (epilep* or convuls* or seizure*).ti.ab.
7 or/5-6
8 and/4,7
9 exp animals/not humans.sh.
10 8 not 9
11 limit 10 to yr="2010 -Current"

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