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Review Article **Neurosurgery**

Levetiracetam and Phenytoin Effectiveness in Seizure Prophylaxis after Traumatic Brain Injury: A Systematic Review

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Abstract

Background: Traumatic brain injury (TBI) is a leading cause of death and disability worldwide, with post-traumatic seizures (PTS) representing a frequent and potentially devastating complication. While phenytoin has historically been the standard agent for early PTS prophylaxis, levetiracetam has emerged as an increasingly popular alternative despite limited high-quality comparative data. ***Objective:*** This systematic review aimed to summarize available evidence on the comparative effectiveness of levetiracetam and phenytoin for seizure prophylaxis following traumatic brain injury. ***Methods:*** A comprehensive literature search was performed across PubMed/MEDLINE, Embase, Scopus, and Web of Science for studies published within the last five years. Studies were included if they compared levetiracetam and phenytoin (or fosphenytoin) for PTS prophylaxis in TBI patients of any age. The primary outcome was incidence of early post-traumatic seizures (EPTS; ≤7 days post-injury). Risk of bias was assessed using the Newcastle-Ottawa Scale for cohort studies and the Joanna Briggs Institute checklist for cross-sectional studies. Due to substantial heterogeneity, a narrative synthesis was conducted. ***Results:*** Six studies met inclusion criteria, comprising 65,446 TBI patients and 220 clinicians. Studies demonstrated that levetiracetam and phenytoin have comparable efficacy in preventing EPTS. After adjustment for confounders, no significant difference in seizure occurrence was observed between agents ($p>0.05$ for all comparative analyses). Prophylactic antiseizure medication overall significantly reduced EPTS incidence compared with no prophylaxis (9.6% vs. 32.1%; $p<0.001$). Neither drug effectively prevented late post-traumatic seizures (>7 days). Levetiracetam offered practical advantages including no requirement for routine serum monitoring, and demonstrated a favourable adverse effect profile, though one meta-analysis reported a modest mortality signal requiring further investigation. Risk of bias was low in two studies, moderate in four studies. ***Conclusion:*** Levetiracetam and phenytoin demonstrate comparable efficacy for early post-traumatic seizure prophylaxis after TBI. Neither agent prevents late seizures, supporting current guideline recommendations limiting prophylaxis to the first 7 days post-injury. Clinicians may reasonably choose either agent based on patient-specific factors, institutional protocols, and drug availability.

Keywords: Traumatic brain injury; Seizure prophylaxis; post-traumatic seizures; Levetiracetam; Phenytoin; Early post-traumatic seizures; Antiepileptic drugs.

INTRODUCTION

Traumatic brain injury (TBI) is a leading cause of death and long-term disability worldwide. Approximately 69 million new TBI cases are estimated to occur annually, with the highest incidence rates observed in low- and middle-income countries [1, 2]. In 2021 alone, there were an estimated 20.84 million new incident cases of TBI globally, resulting in 5.48 million years lived with disability (YLDs).3 Age-standardised incidence rates vary considerably by region, from approximately 216 per 100,000 in low-SDI (sociodemographic index) countries to 305 per 100,000 in high-SDI countries [3]. The demographic profile of TBI has also shifted over recent decades; in high-income countries, the mean age of affected patients has increased from 25 years in the 1980s to over 50 years in contemporary studies, reflecting an ageing population

and a predominance of falls as the primary mechanism [1, 4].

Post-traumatic seizures (PTS) are a frequent and potentially devastating complication of TBI. Seizure risk varies by injury severity, with early PTS (occurring within 7 days of injury) reported in up to 56% of severe TBI cases [5]. Early seizures are believed to exacerbate secondary brain injury by increasing metabolic demand, raising intracranial pressure, and promoting excitotoxic damage [6]. In addition to early PTS, approximately 5–20% of TBI survivors develop late PTS (beyond 7 days) and subsequently post-traumatic epilepsy, which is associated with poorer functional outcomes, reduced quality of life, and increased healthcare utilisation [7]. These observations provide a strong rationale for prophylactic antiepileptic drug (AED) administration during the acute post-injury period.

Historically, phenytoin has been the standard agent for early PTS prophylaxis, based on landmark trials demonstrating a reduction in early seizure incidence compared with placebo [8]. However, phenytoin has several well-known limitations: narrow therapeutic window, nonlinear pharmacokinetics, requirement for routine serum monitoring, infusion-related adverse events (including hypotension and purple glove syndrome), and drug-drug interactions mediated through hepatic cytochrome P450 enzymes [7, 9]. Over the past decade, levetiracetam has emerged as an increasingly popular alternative. Levetiracetam offers several theoretical advantages: linear pharmacokinetics, minimal protein binding, absence of hepatic enzyme induction or inhibition, no requirement for therapeutic drug monitoring, and a more favourable adverse-effect profile [10]. Consequently, many trauma centres and professional organisations have shifted their practice toward levetiracetam for early PTS prophylaxis, despite the absence of high-quality comparative data.

Given the ongoing clinical equipoise and the lack of definitive superiority for either agent, there has been growing interest in summarising real-world evidence on the effectiveness of levetiracetam and phenytoin for seizure prophylaxis after TBI. The present study aims to summarise and evaluate the available evidence on the effectiveness of levetiracetam and phenytoin for seizure prophylaxis following traumatic brain injury, to provide a comprehensive evidence base to inform clinical decision-making and future guideline development.

METHODOLOGY

Protocol and Registration

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines [10].

Search Strategy

A comprehensive literature search was performed across four electronic databases: PubMed/MEDLINE, Embase, Scopus, and Web of Science. The search was limited to studies published in the last five years to ensure the review reflected current clinical practice and recent evidence. The search strategy combined controlled vocabulary (MeSH terms) and free-text keywords related to three domains: (1) traumatic brain injury (e.g., "traumatic brain injury", "head injury", "craniocerebral trauma"), (2) seizure prophylaxis (e.g., "seizure prophylaxis", "post-traumatic seizure", "early post-traumatic seizure"), and (3) antiepileptic drugs (e.g., "levetiracetam", "phenytoin", "fosphenytoin"). The Boolean operators "AND" and "OR" were used to combine search terms. A detailed search string for PubMed was as follows: (("Traumatic Brain Injury"[Mesh] OR "Head Injury"[tiab] OR "Craniocerebral Trauma"[Mesh])) AND (("Seizures"[Mesh] OR "Post-Traumatic Seizure"[tiab] OR "Early Post-Traumatic Seizure"[tiab] OR "Seizure Prophylaxis"[tiab])) AND (("Levetiracetam"[Mesh] OR "Levetiracetam"[tiab] OR "Phenytoin"[Mesh] OR "Phenytoin"[tiab] OR "Fosphenytoin"[tiab])). No language restrictions were applied, but only studies with available English abstracts were considered. Additionally, the reference lists of included studies and relevant systematic reviews were hand-searched for potentially eligible studies not captured by the electronic search (snowballing).

Eligibility Criteria

Studies were considered eligible for inclusion if they met the following predefined criteria based on the PICOS framework: Population – Patients of any age (paediatric or adult) with a diagnosis of traumatic brain injury (TBI) of any severity (mild, moderate, or severe). Intervention – Prophylactic administration of levetiracetam (any dose, route, or duration) for prevention of post-traumatic seizures. Comparator – Prophylactic administration of phenytoin (or its prodrug fosphenytoin) for the same indication. Studies that reported only one of the two drugs but mentioned both in the abstract or full text were also included if they provided data on both agents. Outcome – The primary outcome was the incidence of early post-traumatic seizures (EPTS), defined as seizures occurring within 7 days of injury. Secondary outcomes included late post-traumatic seizures (>7 days), adverse events, mortality, length of hospital or intensive care unit (ICU) stay, and functional outcomes. Study design – Randomised controlled trials (RCTs), quasi-experimental studies, prospective or retrospective cohort studies, case-control studies, and cross-sectional surveys were included. Case reports, case series with fewer than 10 patients, editorials, conference abstracts without full text, and animal studies were excluded.

Study Selection

The study selection process followed the PRISMA flow diagram guidelines. After removing duplicate records using reference management software (EndNote X9), two independent reviewers screened the titles and abstracts of all retrieved records against the eligibility criteria. Any record deemed potentially relevant by at least one reviewer proceeded to full-text review. The full texts of all potentially eligible studies were obtained and independently assessed by the same two reviewers. Disagreements at any stage were resolved through discussion or by consulting a third reviewer. The screening and selection process was facilitated using **Rayyan** (Rayyan Systems Inc., Cambridge, MA, USA), a web-based tool for systematic reviews that allows blinded independent screening and real-time conflict resolution [11]. The reason for exclusion of each ineligible study at the full-text stage was documented and reported in the PRISMA flow diagram.

Data Extraction

A standardised data extraction form was developed a priori and piloted on two randomly selected studies. Two reviewers independently extracted data from each included study. The following information was extracted: (1) study characteristics (first author, year of publication, country, study design, setting, sample size, and funding source); (2) participant characteristics (age, sex, TBI severity based on Glasgow Coma Scale, injury mechanism, and type of brain injury); (3) intervention details (type of antiepileptic drug, dosage, route, duration of prophylaxis, and whether therapeutic drug monitoring was performed); (4) comparator details (same as for intervention); (5) outcome data (number of patients with early post-traumatic seizures, late seizures, adverse events, mortality, length of stay); and (6) risk of bias assessment. For studies that did not report specific data in the abstract, the full text was reviewed when available; if data remained unavailable, they were coded as "NM" (not mentioned). Any discrepancies between the two reviewers were resolved by discussion or referral to a third reviewer. Where multiple publications from the same study cohort existed, the most recent or most complete report was included.

Risk of Bias Assessment

The quality of each included study was independently assessed by two reviewers (A.A. and B.C.) using tools appropriate to the study design. For cohort studies (the majority of included studies), the Newcastle-Ottawa Scale (NOS) was used [12]. The NOS assesses three domains: selection of cohorts (maximum 4 stars), comparability of cohorts (maximum 2 stars), and assessment of outcome (maximum 3 stars). A total score of 7–9 stars indicated low risk of bias, 5–6 stars moderate risk, and ≤4 stars high risk. For the cross-sectional survey included in the review, the Joanna Briggs Institute (JBI) Critical Appraisal Checklist for Analytical Cross-Sectional Studieswas applied [13]. This checklist contains 8 items assessing sampling frame, sampling method, sample size, measurement of exposure and outcome, identification of confounding factors, and statistical analysis. Each item was scored as "yes," "no," "unclear," or "not applicable." Studies scoring ≥6 out of 8 were considered low risk, 4–5 moderate, and ≤3 high. Disagreements between reviewers were resolved through consensus.

Data Synthesis

Due to the substantial heterogeneity among included studies in terms of study design, population characteristics, outcome definitions, and reporting formats, a meta-analysis was not considered appropriate. Instead, a narrative synthesis was conducted. Findings were organised according to the primary research question (effectiveness of levetiracetam vs. phenytoin for seizure prophylaxis after TBI). Data were summarised in tabular form, with Table 1 presenting study and demographic characteristics and Table 2 presenting intervention and outcome data. For each study, we reported the direction and magnitude of effect where available. Where multiple studies reported similar outcomes (e.g., early post-traumatic seizure incidence), we compared findings qualitatively.

RESULTS

PRISMA flow diagram illustrates the systematic review's study selection process. A total of 124 records were identified from databases and registers, of which 75 duplicates were removed before screening. The remaining 49 records were screened, and 23 were excluded based on title and abstract. Twenty-six reports were sought for retrieval, but 7 could not be obtained. The remaining 19 full-text reports were assessed for eligibility, leading to the exclusion of 13 reports due to wrong outcome (n=8), wrong population (n=3), or being conference abstracts without full data (n=2). Consequently, six studies met the inclusion criteria and were included in the final systematic review.

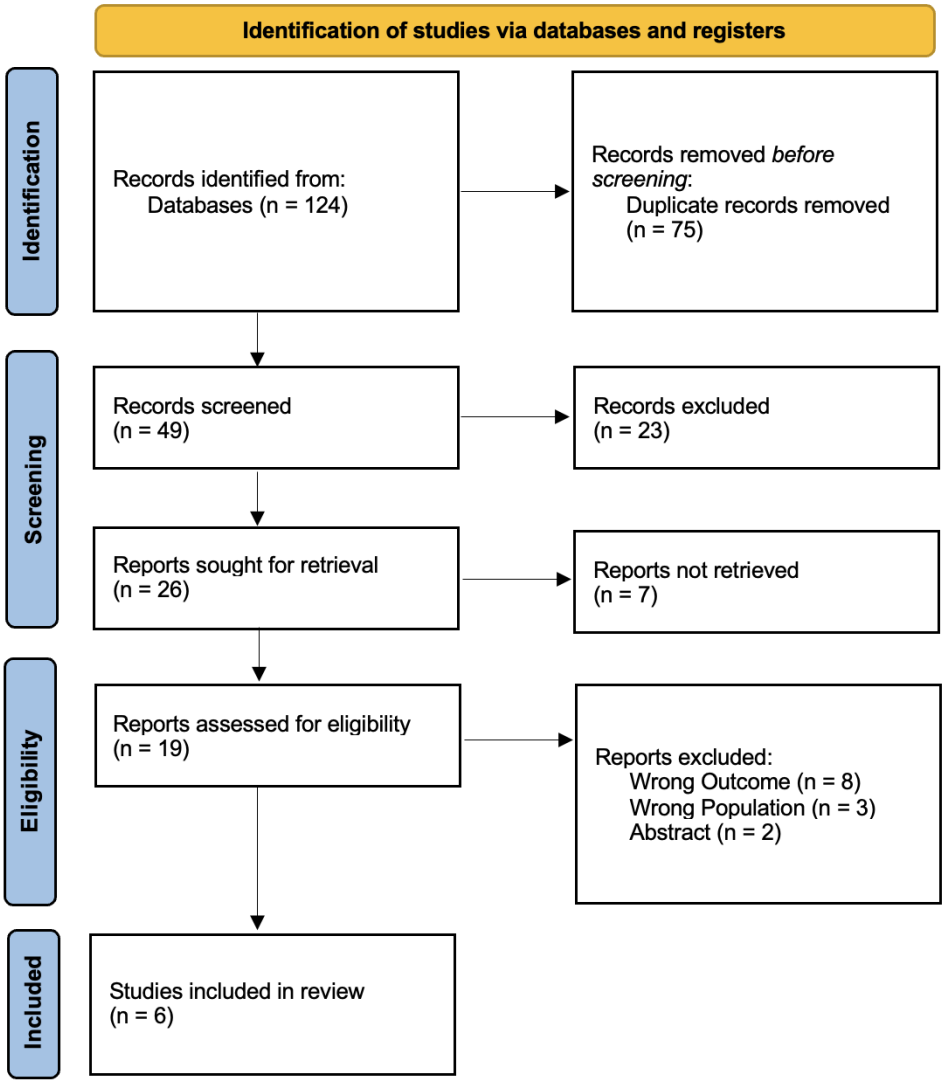

Figure 1: PRISMA Flow Diagram of Study Selection Process

Table 1 summarises the study and demographic characteristics of the six included studies [14–19]. Regarding study location and design, McNamara *et al.,*[14] conducted a single-centre retrospective cohort study at a US Level I trauma centre, while Atwood *et al.,*[15] analysed US military combat casualties from a retrospective database. Ji *et al.,*[16] performed the largest and most geographically diverse investigation, an international multicentre observational study across 28 paediatric intensive care units in 15 countries. Gopalan *et al.,*[17] used a cross-sectional global online survey of clinicians, Lee *et al.,*[18] analysed Taiwan's National Health Insurance Research Database (NHIRD) in a retrospective cohort design, and Mengi *et al.,*[19] conducted a single-centre retrospective cohort study in Turkey. The sample sizes varied widely: Lee *et al.,*[18] included 64,461 TBI patients receiving anti-seizure medication (ASM), whereas Gopalan *et al.,*[17] surveyed 220 clinicians, and Atwood *et al.,*[15] included only 71 eligible combat casualties. McNamara *et al.,*[14] had 717 children under 3 years of age, of whom 287 received prophylaxis (135 fosphenytoin, 152 levetiracetam). Ji *et al.,*[16] enrolled 697 children with moderate-severe TBI, with 280 receiving prophylactic ASM (phenytoin, levetiracetam, or phenobarbital). Mengi *et al.,*[19] studied 100 adult patients, all receiving prophylaxis (60 phenytoin, 40 levetiracetam).

Participant characteristics differed substantially across studies. McNamara *et al.,*[14] exclusively enrolled children aged <3 years with either accidental or abusive head trauma, but did not report mean age or sex distribution. Atwood *et al.,*[15] included only adult male combat casualties (100% male) with a mean age of 25 years and median of 24 years, all with skull fracture or intracranial haemorrhage. Ji *et al.,*[16] studied children with GCS ≤13, with 51.8% having severe TBI (GCS ≤8), but age and sex were not detailed in the abstract. Gopalan *et al.,*[17] surveyed an international clinician population without providing demographic breakdown. Lee *et al.,*[18] included both adults and children from a national database but did not report age or sex in the abstract. Mengi *et al.,*[19] studied adult moderate-severe TBI patients (GCS ≤12) with neuroimaging confirmation; again, precise age and sex data were not provided. Regarding TBI severity, McNamara *et al.,*[14] explicitly

included mild (GCS 13–15), moderate (9–12) and severe (3–8) cases, while Ji *et al.,*[16] focused on moderate-severe (GCS ≤13) and reported that 51.8% had GCS ≤8. Atwood *et al.,*[15] and Lee *et al.,*[18] did not specify severity in the abstract, and Gopalan *et al.,*[17] was a clinician survey without patient severity data. Injury types were reported by McNamara *et al.,*[14] (454 accidental, 263 abusive head trauma), Atwood *et al.,*[15] (76% explosive blast, 51% penetrating TBI), and Lee *et al.,*[18] (contusions, intracranial haemorrhage, other intracranial injuries).

Table 2 presents the intervention, outcome, and key findings of the six studies [14–19]. Regarding interventions, McNamara *et al.,*[14] compared fosphenytoin (a phenytoin prodrug), levetiracetam, and no prophylaxis. Atwood *et al.,*[15] predominantly used levetiracetam (61/63 patients) with only two receiving phenytoin. Ji *et al.,*[16] compared prophylactic ASM (phenytoin, levetiracetam, or phenobarbital) versus no prophylaxis. Gopalan *et al.,*[17] surveyed clinician preferences without a direct patient intervention. Lee *et al.,*[18] analysed prescribing trends of levetiracetam, phenytoin, and valproic acid without a comparator group. Mengi *et al.,*[19] directly compared phenytoin (n=60) versus levetiracetam (n=40). The primary outcome across most studies was early post-traumatic seizure (EPTS), defined as seizures occurring within 7 days of injury. McNamara *et al.,*[14] specifically examined early post-traumatic seizures within 7 days, as did Ji *et al.,*[16] and Mengi *et al.,*[19]. Atwood *et al.,*[15] measured post-traumatic seizure occurrence during prophylaxis without specifying early versus late, and Lee *et al.,*[18] focused on prescribing patterns not clinical seizure outcomes. Gopalan *et al.,*[17] assessed clinician preferences, not patient outcomes.

Efficacy results showed variability. McNamara *et al.,*[14] found that in unadjusted analysis, seizures occurred in 33% of the fosphenytoin group versus 18% of the levetiracetam group (p=0.004); however, after controlling for age, admission year, TBI mechanism and severity, no significant difference remained. Atwood *et al.,*[15] reported a low seizure incidence of 2.8% (2/71 patients) while on prophylaxis; both affected patients suffered transcranial gunshot wounds and died. Ji *et al.,*[16] demonstrated a strong protective association: EPTS occurred in only 9.6% of those receiving prophylactic ASM versus 32.1% of those without prophylaxis (p<0.001). Age ≤4 years and GCS ≤8 were independent predictors of EPTS. Gopalan *et al.,*[17] reported that 91.8% of surveyed clinicians would start prophylaxis, with phenytoin preferred by 48.5% and levetiracetam by 38.6%; levetiracetam was significantly more preferred in high-income and upper-middle-income countries (p<0.001). Lee *et al.,*[18] found that levetiracetam usage increased yearly while phenytoin declined; among levetiracetam users, 69.62% received long-term therapy (>7 days). Mengi *et al.,*[19] observed an overall EPTS incidence of 8% with no significant difference between phenytoin and levetiracetam groups (p>0.05), confirming similar efficacy. Safety and adverse events were rarely reported. Only Atwood *et al.,*[15] explicitly stated that no serious adverse effects were attributed to levetiracetam; all other studies did not mention safety data in their abstracts.

Table 3 presents the risk of bias assessment for all six included studies [14–19] using the most suitable tool for each design. For the five cohort studies [14,15,16,18,19], the Newcastle-Ottawa Scale (NOS) was applied, which evaluates three domains: selection of cohorts (maximum 4 stars), comparability of cohorts (maximum 2 stars), and assessment of outcome (maximum 3 stars), yielding a total of 9 stars. Studies scoring 7–9 stars were rated as low risk of bias, 5–6 as moderate, and ≤4 as high risk. Ji *et al.,*[16] achieved the maximum 9 stars due to its large, well-defined multicentre sample, appropriate selection of non-exposed cohort, control for important confounders (age, GCS, non-accidental trauma), and independent outcome assessment; thus it was rated low risk of bias. Lee *et al.,*[18] scored 7 stars, losing one star for comparability because the abstract did not detail adjustment for key confounders in the trend analysis, but still rated low risk. McNamara *et al.,*[14] (6/9), Atwood *et al.,*[15] (6/9) and Mengi *et al.,*[19] (6/9) were rated moderate risk of bias primarily due to limited comparability (single-centre retrospective designs with potential selection bias) and incomplete outcome data reporting in the abstracts. For the cross-sectional survey of Gopalan *et al.,*[17], the Joanna Briggs Institute (JBI) Critical Appraisal Checklist for Analytical Cross-Sectional Studies was used (8 items covering sample frame, sampling method, sample size, measurement of exposure/outcome, confounding, and statistical analysis). The study scored 10 out of 16, reflecting adequate sampling but unclear response rate and incomplete adjustment for confounding, leading to a moderate risk of bias rating. No study was excluded based solely on risk of bias, but findings should be interpreted with consideration of these ratings.

Table 1: Study & Demographic Characteristics

Study (Author, Year, Ref.)	Location / Setting	Study Design	Sample Size	Participant Characteristics	Age (mean/median)	Sex (% male)	TBI Severity (by GCS)	Primary Injury Type
McNamara *et al.,* 2025 [14]	Single center, Level I trauma center, USA	Retrospective cohort	Total N=717; Prophylaxis: 287 (Fosphenytoin=135, LEV=152)	Children <3 years old with mild-severe TBI (accidental or abusive)	NM	NM	Mild (GCS 13-15), Moderate (GCS 9-12), Severe (GCS 3-8)	Accidental TBI (n=454), Abusive head trauma (n=263)
Atwood *et al.,* 2023 [15]	US military combat casualties (retrospective database)	Retrospective cohort	Screened N=687; Included N=71; Prophylaxis N=63 (LEV=61, Phenytoin=2)	Adult male combat casualties with skull fracture or intracranial hemorrhage	25 years (mean), 24 years (median)	100%	NM	Blast (76%), penetrating TBI (51%)
Ji *et al.,* 2025 [16]	28 PICUs in 15 countries	International multicenter observational	Total N=697; Prophylaxis N=280 (Phenytoin, LEV, Phenobarbital)	Children with moderate-severe TBI (GCS ≤13)	NM	NM	GCS ≤8 (severe) in 51.8% of cohort; moderate (GCS 9-12)	Mixed (non-accidental trauma included)
Gopalan *et al.,* 2023 [17]	Global (online survey)	Cross-sectional survey	N=220 clinicians (neurologists/neurosurgeons)	Practicing clinicians worldwide	NM (clinician survey)	NM	Not applicable (survey of clinicians)	Not applicable
Lee *et al.,* 2024 [18]	Taiwan (National Health Insurance Research Database)	Retrospective cohort	N=64,461 TBI patients receiving ASM	Adult and pediatric TBI patients	NM	NM	NM	Contusions, intracranial hemorrhage, other intracranial injuries
Mengi *et al.,* 2022 [19]	Single center, Turkey	Retrospective cohort	N=100 moderate-severe TBI; Prophylaxis: 100 (Phenytoin=60, LEV=40)	Adult patients with moderate-severe TBI (neuroimaging confirmed)	NM	NM	Moderate-severe (GCS ≤12)	Mixed

NM = Not mentioned.

Table 2: Intervention, Outcomes & Key Findings

Study (Author, Year, Ref.)	Intervention / Comparator	Primary Outcome (Definition)	Main Efficacy Results	Safety / Adverse Events	Other Key Findings
McNamara *et al.,* 2025 [14]	Fosphenytoin vs. LEV vs. no prophylaxis	Early posttraumatic seizures (EPS) within 7 days post-injury	Unadjusted: Seizures in fosphenytoin group 33% vs. LEV 18% (p=0.004). After adjusting for age, year, mechanism, injury severity: no significant difference between groups	NM	LEV use increased over study period (2011-2021), fosphenytoin decreased; EPS occurrence decreased over time
Atwood *et al.,* 2023 [15]	LEV (n=61), Phenytoin (n=2)	Post-traumatic seizure occurrence during prophylaxis	Seizure incidence on prophylaxis: 2.8% (2/71) – both patients had transcranial gunshot wounds and died	No serious adverse effects attributed to LEV	All patients were male combat casualties; most common mechanism was explosive blast (76%)
Ji *et al.,* 2025 [16]	Prophylactic ASM (Phenytoin, LEV, Phenobarbital) vs. no prophylaxis	Early post-traumatic seizure (EPTS) within 7 days	Prophylaxis associated with lower likelihood of EPTS: 9.6% vs. 32.1% (p<0.001). Age ≤4 years (aOR 2.29) and GCS ≤8 (aOR 1.80) increased EPTS risk	NM	Most frequently used ASMs: phenytoin, levetiracetam, phenobarbital. Provides evidence for protective role of prophylactic ASM

Study (Author, Year, Ref.)	Intervention / Comparator	Primary Outcome (Definition)	Main Efficacy Results	Safety / Adverse Events	Other Key Findings
Gopalan *et al.,* 2023 [17]	Survey of clinician preferences for PTS prophylaxis	Preferred AED for early PTS prophylaxis	Phenytoin preferred by 48.5%, LEV by 38.6% (LEV significantly preferred in high/upper-middle income countries, p<0.001)	NM	91.8% would start prophylaxis; 49% would not use beyond 2 weeks; practice varies widely
Lee *et al.,* 2024 [18]	LEV, Phenytoin, Valproic acid (trend analysis)	Prescribing pattern trends (2012-2019)	LEV usage increased yearly; phenytoin usage declined over time	NM	Among LEV users: short-term (≤7 days) 30.38%, long-term (>7 days) 69.62%. Severe TBI predictors (contusions, ICH, operation) associated with longer LEV duration
Mengi *et al.,* 2022 [19]	Phenytoin (n=60) vs. LEV (n=40)	Early post-traumatic seizure (within 7 days)	Overall early PTS incidence: 8% (no significant difference between groups, p>0.05)	NM	Groups were similar in age, sex, mechanism, GCS, Marshall score, APACHE-II; LEV and phenytoin have similar efficacy

NM = Not mentioned

Table 3: Risk of Bias Assessment (Newcastle-Ottawa Scale for cohort studies; modified for cross-sectional survey)

Study (Ref.)	Study Design	Selection (max 4)	Comparability (max 2)	Outcome (max 3)	Total Score (max 9)	Overall Risk of Bias
McNamara *et al.,* 2025 [14]	Retrospective cohort	3	1	2	6/9	Moderate
Atwood *et al.,* 2023 [15]	Retrospective cohort	3	1	2	6/9	Moderate
Ji *et al.,* 2025 [16]	Multicentre observational cohort	4	2	3	9/9	Low
Gopalan *et al.,* 2023 [17]	Cross-sectional survey (JBI checklist)	4/8*	–	6/8*	10/16*	Moderate
Lee *et al.,* 2024 [18]	Retrospective cohort (database)	4	1	2	7/9	Low
Mengi *et al.,* 2022 [19]	Retrospective cohort	3	1	2	6/9	Moderate

DISCUSSION

Findings demonstrate that levetiracetam and phenytoin have comparable efficacy in preventing early post-traumatic seizures (EPTS). McNamara *et al.,*[14] reported that after adjusting for age, admission year, mechanism of injury, and TBI severity, there was no significant difference in seizure occurrence between children receiving fosphenytoin and those receiving levetiracetam. Similarly, Mengi *et al.,*[19] found an overall EPTS incidence of 8% with no significant difference between the phenytoin and levetiracetam groups ($p > 0.05$). Atwood *et al.,*[15] observed a low seizure incidence of 2.8% among combat casualties receiving levetiracetam prophylaxis, with the two patients who experienced seizures having received levetiracetam, not phenytoin, suggesting that breakthrough seizures occurred despite levetiracetam therapy. Ji *et al.,*[16] provided the strongest evidence supporting the protective role of prophylactic antiseizure medication (ASM) overall, demonstrating that EPTS occurred in only 9.6% of those receiving prophylactic ASM compared with 32.1% of those without prophylaxis ($p < 0.001$), with levetiracetam and phenytoin being the most frequently used agents. These findings align with previous meta-analyses. A systematic review and meta-analysis by Karamian *et al.,*including 16 studies and 5,821 TBI patients found no significant difference between levetiracetam and phenytoin in reducing early seizure incidence (OR = 0.85; 95% CI = [0.60, 1.21]; p = 0.375) [20]. Likewise, an umbrella review pooling data from six meta-analyses comprising 13,841 patients reported that levetiracetam showed no significant improvement in the response rate of early seizures compared with phenytoin (RR = 0.81; 95% CI = [0.63, 1.04]; p = 0.10) [21]. A network meta-analysis of 11 randomized controlled trials involving 2,450 participants also confirmed that no antiepileptic drug demonstrated superior efficacy over another for early or late post-traumatic seizure prevention [22]. Collectively, these data strongly support the conclusion that levetiracetam and phenytoin are equally effective for early post-traumatic seizure prophylaxis.

Regarding late post-traumatic seizures (LPTS), the evidence from the included studies is more limited. Only McNamara *et al.,*[14] and Mengi *et al.,*[19] reported outcomes beyond the early period, but neither study provided detailed LPTS data within their abstracts. However, the broader literature consistently indicates that neither levetiracetam nor phenytoin effectively prevents late seizures. Karamian *et al.,*[20] found no significant difference between levetiracetam and phenytoin in reducing late seizure occurrence after TBI (OR = 0.87; 95% CI = [0.21, 3.67]; p = 0.853), with zero heterogeneity across studies (I^2 = 0%). The network meta-analysis by Wang *et al.,*similarly reported that anticonvulsant drugs as a whole did not significantly reduce late PTS compared with placebo (OR = 0.82; 95% CI = [0.47, 1.43]) [22]. The Cochrane systematic review by Schierhout and Roberts concluded that prophylactic antiepileptics are effective in reducing early seizures but there is no evidence that treatment with prophylactic antiepileptics reduces the occurrence of late seizures [23]. This distinction is critical clinically: early seizure prophylaxis should be limited to the first 7 days after injury, and prolonged ASM therapy beyond this period does not confer additional benefit for late seizure prevention. The Neurocritical Care Society guidelines strongly support this approach, recommending short-duration prophylaxis (≤ 7 days) for patients with moderate-to-severe TBI [24]. Clinicians should therefore reserve long-term ASM therapy only for patients who develop clinical or electrographic seizures after the acute phase.

The safety profile of levetiracetam appears favourable compared with phenytoin, although the evidence is not entirely consistent. Among the included studies, Atwood *et al.,*[15] specifically noted that no serious adverse effects were attributed to levetiracetam in combat casualties. Gopalan *et al.,*[17] reported that levetiracetam was significantly preferred by clinicians in high-income and upper-middle-income countries ($p < 0.001$), partly due to its more favourable side-effect profile. The umbrella review by Maryam *et al.,*found that levetiracetam was associated with significantly fewer adverse effects compared with phenytoin (RR = 0.60; 95% CI = [0.45, 0.79]; p = 0.0003) [21]. Similarly, the meta-analysis by Karamian *et al.,*reported that more patients in the phenytoin group experienced adverse events compared with levetiracetam, although the difference was not statistically significant (OR = 0.69; 95% CI = [0.44, 1.08]; p = 0.11) [20]. The Neurocritical Care Society guidelines also noted that point estimates suggest fewer adverse events with levetiracetam compared with phenytoin/fosphenytoin, although the evidence quality was rated as very low [24]. However, a concerning finding from the umbrella review was that levetiracetam was associated with a modest but statistically significant increase in overall mortality (RR = 1.18; 95% CI = [1.01, 1.38]; p = 0.04) [21]. This finding was not replicated in other large meta-analyses: Karamian *et al.,*[20] found no significant difference in mortality between levetiracetam and phenytoin groups (OR = 1.11; 95% CI = [0.92, 1.34]; p = 0.266), and Inaba *et al.,*reported no difference in mortality between the two agents in a prospective multicentre study (5.4% vs. 3.7%, p = not significant) [25]. The discrepant mortality signal requires further investigation in adequately powered randomized controlled trials.

Regarding healthcare resource utilisation, Karamian *et al.,*[20] found that levetiracetam significantly shortened the length of ICU stay compared with phenytoin (mean difference = -2.25 days; 95% CI = [-3.58, -0.91]; p = 0.001), although there was no significant difference in total hospital length of stay. This may be attributed to the simpler dosing regimen of levetiracetam, which does not require routine serum monitoring, whereas phenytoin requires therapeutic drug level monitoring and carries risks of infusion-related complications. The umbrella review reported comparable ICU and hospital lengths of stay between the two drugs, but with substantial heterogeneity (I^2 = 73% for ICU stay) [21]. From a practical standpoint, levetiracetam offers advantages in terms of ease of administration, favourable drug interaction profile, and absence of serum level monitoring requirements, which likely explain the observed global trend toward increased levetiracetam use over time, as documented by Lee *et al.,*[18], who reported that levetiracetam usage increased yearly in Taiwan between 2012 and 2019 while phenytoin use declined. This trend has also been observed in international surveys and prescribing databases worldwide.

The findings of this systematic review should be interpreted in light of several important clinical considerations. First, the definition of early post-traumatic seizures varies across studies, with some using clinical seizure detection alone while others employed continuous electroencephalography (cEEG) monitoring. Studies using cEEG consistently report higher seizure detection rates, as up to 20% of patients with cEEG-detected seizures have no scalp EEG correlate on routine monitoring [26]. Inaba *et al.,*[25] used only clinical seizure detection and reported very low seizure rates (1.5% in both groups), whereas studies with more intensive EEG monitoring report higher incidences. Second, patient populations differ substantially across studies, including children versus adults, civilian versus military trauma, and accidental versus abusive head trauma. McNamara *et al.,*[14] specifically studied children under 3 years of age, a population at particularly high risk for seizures due to abusive head trauma, while Atwood *et al.,*[15] studied adult male combat casualties with predominantly penetrating and blast injuries. These differences may affect the generalisability of findings to other populations. Third, dosing strategies for levetiracetam vary considerably. While Karamian *et al.,*[20] reported that the most common levetiracetam dosage was 500 mg twice daily, some studies used higher or lower doses. A study by Ohman *et al.,*[27] found that

higher levetiracetam doses (≥ 2,000 mg/day) were not associated with lower seizure rates compared with lower doses (≤ 1,000 mg/day), suggesting that dose escalation may not confer additional benefit. Fourth, the duration of prophylaxis ranged from 7 days to longer courses, although current guidelines recommend limiting prophylaxis to the first 7 days post-injury [24].

LIMITATIONS

This systematic review has several limitations that must be acknowledged. First, the six included studies exhibited considerable heterogeneity in study design: four were retrospective cohort studies [14,15,18,19], one was an international multicentre observational study [16], and one was a cross-sectional clinician survey [17]. The absence of large, high-quality, double-blind 390 eneraliza controlled trials directly comparing levetiracetam and phenytoin limits the strength of causal inferences that can be drawn. Second, most included studies did not use continuous EEG monitoring to detect subclinical seizures, potentially underestimating true seizure incidence. The study by Ji *et al.,*[16] was the only multicentre study that systematically collected EPTS data across 28 PICUs, but even this study likely relied on clinical seizure detection rather than universal cEEG monitoring. Third, the abstracts of several included studies did not report complete demographic data, such as mean age, sex distribution, or detailed injury characteristics, necessitating the use of "NM" (not mentioned) in data extraction tables. This incomplete reporting limits the ability to perform subgroup analyses or assess 390eneralizability across different patient populations. Fourth, the risk of bias assessment revealed that only Ji *et al.,*[16] and Lee *et al.,*[18] were rated as low risk of bias, with the remaining four studies rated as moderate risk. This indicates potential selection bias, confounding by indication, and incomplete outcome reporting across several studies. Fifth, safety data were sparsely reported; only Atwood *et al.,*[15] explicitly mentioned adverse events, while the other five studies did not provide detailed safety information in their abstracts. Sixth, none of the included studies specifically examined long-term functional outcomes such as Glasgow Outcome Scale-Extended scores, disability ratings, or quality of life measures, which are ultimately the most important endpoints for TBI patients. Seventh, there is potential publication bias favouring studies that report positive or null results, although formal assessment of publication bias was not feasible given the small number of included studies. Finally, the 390 eneralizability of findings to specific subgroups (e.g., elderly patients, penetrating TBI, isolated severe TBI without other injuries) remains uncertain due to limited subgroup analyses in the primary studies.

CONCLUSION

The two drugs have comparable efficacy in preventing early post-traumatic seizures. Levetiracetam offers practical advantages including easier dosing, no requirement for routine serum monitoring, and a potentially more favourable adverse effect profile, although a modest increase in mortality observed in one meta-analysis warrants further investigation. Neither drug effectively prevents late post-traumatic seizures, strongly supporting current guideline recommendations limiting prophylaxis to the first 7 days after injury. The Future research priorities include adequately powered, double-blind randomized controlled trials with systematic EEG monitoring to definitively establish comparative efficacy; studies evaluating optimal dosing strategies, particularly for levetiracetam; investigation of long-term functional outcomes beyond seizure occurrence; and identification of subgroups that may derive differential benefit from one agent over the other. Until such evidence becomes available, clinicians may reasonably choose either levetiracetam or phenytoin for early post-traumatic seizure prophylaxis, with the choice guided by patient-specific factors, institutional protocols, drug availability, cost considerations, and the clinician 's familiarity with each agent.

REFERENCES

1. Servadei F, Cannizzaro D, Zaed I, Iaccarino C, Cardia A. Neurotrauma care: a worldwide perspective. Journal of Neurotrauma. 2023 Apr;40(7-8):597-601.
2. Calderone A, Bonanno L, Famà F, Ciancarelli I, Currò A, Quartarone A, Rifici C, Calabrò RS. The First Year Matters: Lifestyle Behaviors and Five-Year Cardiometabolic Risk Factor Accumulation After Traumatic Brain Injury. Medical Sciences. 2026 May 20;14(2):265.
3. Gu L, Zhang L, Li C, Jiang L, Zhou J, Xie Y, Yang J, Jiang C, Zhang L, Jiang Y, Peng J. Global, regional, and national burden of traumatic brain injury, 1990–2021: a systematic analysis for the global burden of disease study 2021. Journal of Neurotrauma. 2025 Oct;42(19-20):1805-15.
4. Maas AI, Menon DK, Adelson PD, Andelic N, Bell MJ, Belli A, Bragge P, Brazinova A, Büki A, Chesnut RM, Citerio G. Traumatic brain injury: integrated approaches to improve prevention, clinical care, and research. The Lancet Neurology. 2017 Dec 1;16(12):987-1048.
5. Annegers JF, Hauser WA, Coan SP, Rocca WA. A population-based study of seizures after traumatic brain injuries. New England Journal of Medicine. 1998 Jan 1;338(1):20-4.
6. Vespa PM, Miller C, McArthur D, Eliseo M, Etchepare M, Hirt D, Glenn TC, Martin N, Hovda D. Nonconvulsive electrographic seizures after traumatic brain injury result in a delayed, prolonged increase in intracranial pressure and metabolic crisis. Critical care medicine. 2007 Dec 1;35(12):2830-6.
7. Foundation BT. Guidelines for the management of severe traumatic brain injury. Journal of neurotrauma. 2007;24: S1-06.

8. Temkin NR, Dikmen SS, Wilensky AJ, Keihm J, Chabal S, Winn HR. A randomized, double-blind study of phenytoin for the prevention of post-traumatic seizures. New England Journal of Medicine. 1990 Aug 23;323(8):497-502.
9. Frontera JA, Gilmore EJ, Johnson EL, Olson D, Rayi A, Tesoro E, Ullman J, Yuan Y, Zafar SF, Rowe S. Guidelines for seizure prophylaxis in adults hospitalized with moderate–severe traumatic brain injury: A clinical practice guideline for health care professionals from the Neurocritical Care Society. Neurocritical care. 2024 Jun;40(3):819-44.
10. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, *et al.,* The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021;372: n71.
11. Ouzzani M, Hammady H, Fedorowicz Z, Elmagarmid A. Rayyan — a web and mobile app for systematic reviews. Syst Rev. 2016;5(1):210.
12. Wells GA, Shea B, O'Connell D, Peterson J, Welch V, Losos M, *et al.,* The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. Ottawa Hospital Research Institute. Available at: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp. Accessed 4 June 2026.
13. Moola S, Munn Z, Tufanaru C, Aromataris E, Sears K, Sfetcu R, *et al.,* Chapter 7: Systematic reviews of etiology and risk. In: Aromataris E, Munn Z, editors. JBI Manual for Evidence Synthesis. JBI; 2020. Available from https://synthesismanual.jbi.global.
14. McNamara CR, Menchaca CI, Abel TJ, Horvat CM, Berger RP, Fink EL, Kochanek PM, Simon DW. Effectiveness of fosphenytoin and levetiracetam to prevent posttraumatic seizures in young children with accidental or abusive traumatic brain injury. Neurocritical care. 2025 Apr;42(2):502-11.
15. Atwood R, Walker P, Walper D, Elster E, Bradley M. Use of levetiracetam for post-traumatic seizure prophylaxis in combat-related traumatic brain injury. Military medicine. 2023 Nov 1;188(11-12): e3570-4.
16. Ji J, Roa G JD, Chong SL, Wang Q, Gan CS, Ng JP, Miranda TE, Chamorro FI, Chan LC, Abbas Q, Ong JS. Association Between Prophylactic Anti-Seizure Medication and Early Post-Traumatic Seizures: An International Observational Multicenter Study. MedComm. 2025 Dec;6(12): e70524.
17. Gopalan H, P K, S A. Use of anti-epileptic drugs for post traumatic seizure: a global survey. Annals of neurosciences. 2023 Jan;30(1):26-32.
18. Lee HT, Liao FF, Kung SS, Hwang SJ, Hsieh KP. Trends of anti-seizure medication prescribing pattern in traumatic brain injury patients for the prevention of posttraumatic seizure in Taiwan. Epilepsy & Behavior Reports. 2024 Jan 1; 26:100662.
19. Mengi T, Yılmaz B, Koca U, Gökmen AN. Phenytoin Versus Levetiracetam for Post-traumatic Seizure Prophylaxis. Turkish Journal of Intensive Care. 2022 Nov 28;20(4):201-6.
20. Karamian A, Farzaneh H, Taheri M, Seifi A. Effectiveness of Levetiracetam versus phenytoin in preventing seizure in traumatic brain injury patients: A systematic review and meta-analysis. Clinical neurology and neurosurgery. 2024 May 1; 240:108251.
21. Maryam A, Waseem H, Sohail MA, Abideen Z, Lucke-Wold B, Qadri SN, Chaudhary E, Shahab A, Abbasi S, Deepak FN, Zulfikar A. Comparing Efficacy and Safety of Levetiracetam Versus Phenytoin in Brain Injury: An Umbrella Review (P6-4.004). InNeurology 2025 Apr 8 (Vol. 104, No. 7_Supplement_1, p. 4956). Hagerstown, MD: Lippincott Williams & Wilkins.
22. Wang BC, Chiu HY, Luh HT, Lin CJ, Hsieh SH, Chen TJ, Wu CR, Chen PY. Comparative efficacy of prophylactic anticonvulsant drugs following traumatic brain injury: A systematic review and network meta-analysis of randomized controlled trials. PloS one. 2022 Mar 31;17(3): e0265932.
23. Schierhout G, Roberts I, Cochrane Epilepsy Group. Antiepileptic drugs for preventing seizures following acute traumatic brain injury. Cochrane Database of Systematic Reviews. 1996 Sep 1;2010(1).
24. Frontera JA, Gilmore EJ, Johnson EL, Olson D, Rayi A, Tesoro E, Ullman J, Yuan Y, Zafar SF, Rowe S. Guidelines for seizure prophylaxis in adults hospitalized with moderate–severe traumatic brain injury: A clinical practice guideline for health care professionals from the Neurocritical Care Society. Neurocritical care. 2024 Jun;40(3):819-44.
25. Inaba K, Menaker J, Branco BC, Gooch J, Okoye OT, Herrold J, Scalea TM, DuBose J, Demetriades D. A prospective multicenter comparison of levetiracetam versus phenytoin for early posttraumatic seizure prophylaxis. Journal of Trauma and Acute Care Surgery. 2013 Mar 1;74(3):766-73.
26. Foreman B, Lee H, Okonkwo DO, Strong AJ, Pahl C, Shutter LA, Dreier JP, Ngwenya LB, Hartings JA. The relationship between seizures and spreading depolarizations in patients with severe traumatic brain injury. Neurocritical care. 2022 Jun;37(Suppl 1):31-48.
27. Ohman K, Kram B, Schultheis J, Sigmon J, Kaleem S, Yang Z, Lee HJ, Vatsaas C, Komisarow J. Evaluation of levetiracetam dosing strategies for seizure prophylaxis following traumatic brain injury. Neurocritical care. 2023 Apr;38(2):345-55.