REVIEW

Association of Early Seizure Prophylaxis With Posttraumatic Seizures and Mortality

A Meta-analysis With Evidence Quality Assessment

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Abstract

Purpose of the Review

To evaluate the quality of evidence about the association of primary seizure prophylaxis with antiseizure medication (ASM) within 7 days postinjury and the 18- or 24-month epilepsy/late seizure risk or all-cause mortality in adults with new-onset traumatic brain injury (TBI), in addition to early seizure risk.

Results

Twenty-three studies met the inclusion criteria (7 randomized and 16 nonrandomized studies). We analyzed 9,202 patients, including 4,390 in the exposed group and 4,812 in the unexposed group (894 in placebo and 3,918 in no ASM groups). There was a moderate to serious bias risk based on our assessment. Within the limitations of existing studies, our data revealed a lower risk for early seizures in the ASM prophylaxis group compared with placebo or no ASM prophylaxis (risk ratio [RR] 0.43, 95% confidence interval [CI] 0.33–0.57, $p < 0.00001$, $I^2 = 3\%$). We identified high-quality evidence in favor of acute, short-term primary ASM use to prevent early seizures. Early ASM prophylaxis was not associated with a substantial difference in the 18- or 24-month risk of epilepsy/late seizures (RR 1.01, 95% CI 0.61–1.68, $p = 0.96$, $I^2 = 63\%$) or mortality (RR 1.16, 95% CI 0.89–1.51, $p = 0.26$, $I^2 = 0\%$). There was no evidence of strong publication bias for each main outcome. The overall quality of evidence was low and moderate for post-TBI epilepsy risk and all-cause mortality, respectively.

Summary

Our data suggest that the evidence showing no association between early ASM use and 18- or 24-month epilepsy risk in adults with new-onset TBI was of low quality. The analysis indicated a moderate quality for the evidence showing no effect on all-cause mortality. Therefore, higher-quality evidence is needed as a supplement for stronger recommendations.

Traumatic brain injuries (TBIs) are a significant burden on the global health care system. There are approximately 50 million annual cases of TBI globally, leading to many adverse outcomes and fatalities.[1] TBI costs about US$ 400 billion to the global economy annually.[2] Health care improvement has increased life expectancy worldwide, and many clinicians and researchers have recognized the increasing trends in TBI incidence over the last 20 years, especially among elderly patients experiencing fall-related TBI.[3-6]

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Posttraumatic seizures (PTSs) are known complications of TBI.[7] They may result in secondary brain injury, predispose to brain herniation and death, and predict posttraumatic long-term epilepsy, which refers to recurrent and unprovoked PTSs that occur at least 1 week beyond a TBI and significantly negatively influence patients' quality of life.[8,9] Therefore, primary seizure prophylaxis is routinely considered in moderate to severe TBI to mitigate the risk of PTS and maximize the potential benefits of protecting the brain from secondary injury.

The current guideline recommends primary prophylactic use of antiseizure medications (ASMs) in patients with TBI during the first 7 days postinjury, particularly in moderate to severe cases or when the overall benefit is felt to outweigh the risks associated with such treatment.[10] Although the central role of prophylaxis is to minimize brain damage by preventing early seizures, ASMs are also associated with neurobehavioral and other side effects ranging from fever to benign skin rashes and more severe toxic epidermal necrolysis.[11] In addition, their effect on mortality is also unclear. Evaluating the effectiveness, overall benefit, and potential harms of ASMs used to prevent PTS is essential. Besides, the current recommendation may not be generalized to many vulnerable subgroups, e.g., the elderly population or those systematically excluded or minimally represented in clinical trials and cohorts.

After previous meta-analysis, additional studies have evaluated the effectiveness or safety of primary ASM prophylaxis post-TBI and they have to be considered.[12-14] The current clinical practice is exclusively based on studies of older-generation ASMs, and it seems timely to carefully review the possible gaps in the evidence. Thus, the purpose of this study was to evaluate the evidence quality regarding the association of early ASM use on all-cause mortality and primary prophylaxis of seizures in adults with TBI, providing some insights using a large and representative group of patients.

Methods

Study Design

We evaluated the evidence quality after performing a comprehensive systematic review with meta-analysis of the available scientific literature. We followed the preferred reporting items for systematic reviews and meta-analysis (PRISMA) guidelines.[15] The PROSPERO registry code was CRD42022313904.

Data Sources and Search Strategy

We developed the search strategy following the PRISMA reporting guidelines (detailed in Figure 1), conducting a systematic search in Ovid MEDLINE, ScienceDirect, and Cochrane Library with the combination of search keys and MeSH terms for traumatic brain injury, ASMs, posttraumatic seizure, prophylaxis, and mortality (eTable 1, links.lww.com/CPJ/A408). We also obtained additional studies from contact with neurocritical care field experts and citation searching in pertinent reviews.[12-14] Our search for eligible studies lasted from January 1, 2022, until March 11, 2022.

Eligibility and Exclusion Criteria

We searched for full-text randomized and nonrandomized studies without restricting the year of publication or language. Publications were eligible if (1) they enrolled patients presenting with new-onset mild to severe TBI or post-TBI cranial surgery status, with TBI severity based on Glasgow Coma Scale score (GCS): 3–7 (severe), 8–12 (moderate), and 13–15 (mild)[16]; (2) an exposed group receiving primary prophylaxis with ASM; (3) an unexposed group receiving placebo or no ASM; and (4) assessed early seizures (until 7 days post-TBI), epilepsy (after 7 days post-TBI) incidence as effectiveness outcomes, and/or all-cause mortality risk as a safety outcome. We excluded studies that met the following criteria: (1) had a majority of individuals under 18 years old, (2) compared two ASM treatments, (3) did not have an unexposed group, (4) included individuals who had previously used ASM or had epilepsy before TBI, and (5) were case series, case-control, or cross-sectional studies.

Outcomes and Data Extraction

Our aim focused on evaluating the overall quality of evidence regarding the association of early ASM use with new-onset post-TBI epilepsy/late seizures and all-cause mortality, in addition to early seizure incidence. Either clinical features or electroencephalogram (EEG) findings defined seizures. Using standardized forms created in Microsoft Excel, we extracted relevant values to calculate the effect size (difference of means between the groups) in pooled risk ratio (RR) and summarize the population features and studies' methodology.

Risk-of-Bias Assessment

We defined as risk of bias any systematic distortion that could have influenced the relationship between early ASM prophylaxis and clinical outcomes (such as early seizures, epilepsy/late seizures, and mortality). We performed the risk-of-bias assessment for randomized controlled trials (RCTs) with the Cochrane Collaboration's tool (RoB2).[17] Each study had items evaluated for the randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result. On this scale, we rated each study as low risk, some concerns (similar to moderate risk), or high risk of bias.

We assessed the risk of bias for nonrandomized studies using the ROBINS-I tool.[18] The possible risk-of-bias judgment domains are confounding, selection of participants in the study, classification of interventions, deviations from intended interventions, missing data, measurement of outcomes, and selection of the reported result. On this scale, we rated each study as (1) low risk (the study is comparable to a well-performed randomized trial), (2) moderate risk (the study is sound for a nonrandomized study in at least 1 domain but

cannot be considered comparable to a well-performed randomized trial), (3) serious risk (the study has some crucial problems in at least 1 domain), and (4) critical risk of bias (the study is too problematic in at least 1 domain to provide any valid evidence on the effects of an intervention).

Statistical Analysis

The pooled results comprised the effect sizes of effectiveness and safety outcomes with 95% confidence intervals (CIs). RR was the summary measure for dichotomous outcomes. The Cochran Q test and I^2 statistics assessed the heterogeneity, classified as low (I^2 < 30%), moderate (I^2 ≥ 30%), substantial (I^2 ≥ 50%), or considerable (I^2 ≥ 75%).[19] We used the DerSimonian and Laird random-effects model to calculate pooled estimates because we assumed that the true effect size might differ across studies. When available, we also expected to perform an analysis with the generic variance method using adjusted risk estimates from nonrandomized studies reporting their RR and respective CI or standard errors (SEs).

We stratified in randomized and nonrandomized studies to investigate potential sources of heterogeneity. We conducted meta-regressions to analyze the effect of treatment duration (in days) on new-onset epilepsy and all-cause mortality risk. Further sensitivity analysis included data restricted to (1) studies with low or moderate risk of bias and (2) studies with patients with moderate to severe TBI. We performed a subanalysis for epilepsy and all-cause mortality outcomes, including studies with a longer follow-up duration of 18–24 months to account for varying lengths of follow-up time. To assess potential confounding, we expected to perform multiple other subanalyses for each primary variable when patient-level data were available, including information about the outcomes in patients with (1) epidural hematoma, (2) subdural hematoma, (3) parenchymal contusions, (4) cortical contusion, (5) penetrating brain injury, (6) diffuse axonal injury, or (7) comorbidities such as diabetes mellitus and systemic arterial hypertension.

We assessed publication bias with funnel plot analysis of the primary outcomes and evaluated the symmetrical distribution of trials with similar weights**.** The Review Manager software program (RevMan 5.4; the Nordic Cochrane Center, Copenhagen, Denmark) provided the pooled data results and funnel plots. We performed meta-regression using Stata 17.0 (StataCorp, College Station, TX).

Evidence Quality Rating

To rate the overall quality of evidence, we used the GRADE system for each outcome, stratifying by randomized or nonrandomized studies, sensitivity, and subanalysis.[20] The GRADE classification was downgraded from high quality for each factor that we encountered: (1) high, serious, or critical risk of bias, (2) inconsistency of results (substantial or higher heterogeneity; lack of point estimates similarities among the studies; and minimal or overlap among CIs), (3) imprecision (<400 participants for each outcome and width of the 95% CI), and (4) evidence of publication bias. The GRADE classification was upgraded based on the study design (randomized) and large or higher effect (RR either >2.0 or <0.5).

We did not consider the indirectness criterion in this review because we included a specific population with relevant outcomes and direct comparisons. When only single studies were available, we downgraded the evidence from studies with fewer than 400 participants for inconsistency and imprecision (i.e., sparse data) and rated as low-quality evidence. The evidence could be further downgraded to very low quality if the study presented serious or higher risk of bias.

We defined the quality of evidence as (1) high (further research is unlikely to change our confidence in the estimate of effect), (2) moderate (further research is likely to have a significant effect on our confidence in the estimate of effect and may change the estimate), (3) low (further research is very likely to have a significant effect on our confidence in the estimate of effect and is likely to change the estimate), and (4) very low (we are uncertain about the estimate).

Results

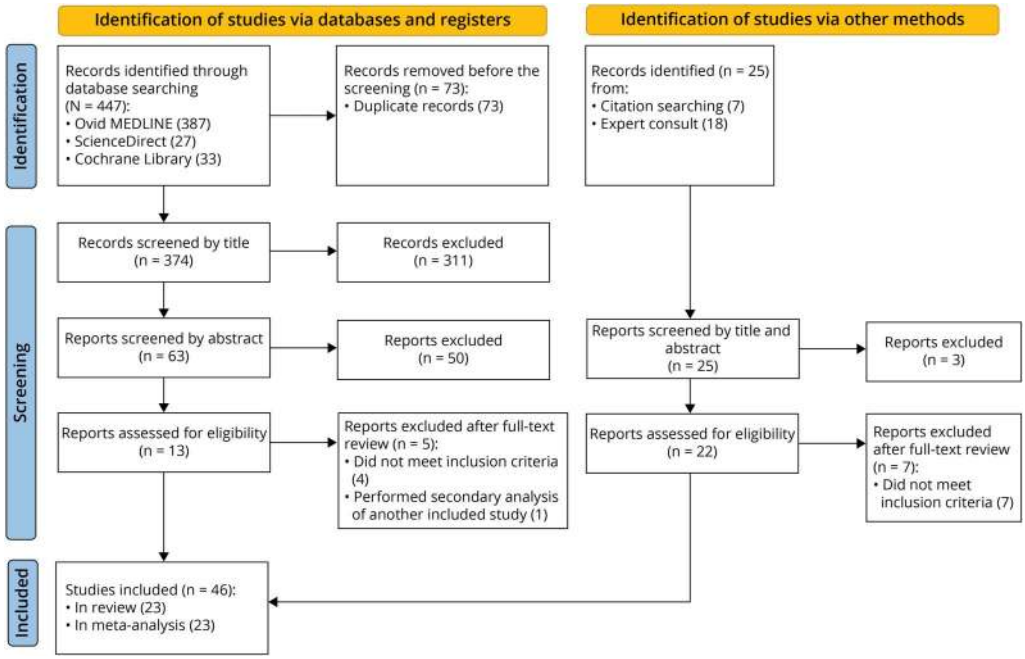
The initial search through the databases yielded 447 studies. After removing duplicates, we screened 374 titles and 63 abstracts, assessing 13 studies through a full-text review. Citation searching and expert consultation identified 25 articles. A total of 23 studies met the eligibility criteria, comprising 9,202 patients from 7 RCTs and 16 nonrandomized studies (Figure 1).[21-43]

Young et al. reported their results in 3 separate analyses: early seizures and all-cause mortality (first report), epilepsy (second report), and epilepsy in participants aged <17 years (third report).[27] We analyzed only the first and second reports in this study because the third population did not meet our age requirement. Formisano et al. reported on 2 independent studies: 1 retrospective and 1 prospective, each observing a separate population; we included them separately.[31] Table 1 details some key features of included studies, and eTable 2 (links.lww.com/CPJ/A408) summarizes the studies excluded after a full-text review.

A total of 4,390 (47.7%) patients received primary ASM prophylaxis after TBI, and 4,812 (52.3%, 894 on placebo, and 3,918 on ASM) were in the unexposed group. Eleven studies included patients with any TBI, and 13 had either moderate to severe or only severe cases. Seizure definition included both clinical and, when available, electrographic seizures. The mean, median, and range of participants' age are shown in Table 1. The follow-up period varied from 1 week to 13 years. Two studies did not disclose enough information to determine their follow-up duration.[28,32]

The commonly used ASMs were phenytoin, levetiracetam, carbamazepine, valproate, and phenobarbital. The timing of

Figure 1 PRISMA Flowchart of Study Screening and Selection



PRISMA = preferred reporting items for systematic reviews and meta-analysis.

medication initiation and the loading and maintenance doses for ASMs were similar across the studies evaluating the same ASM. Unfortunately, multiple subanalyses for each primary variable, including the selected and prespecified groups, were not possible due to a few studies providing patient-level data. Besides that, because no observational study reported their risk estimates, the adjusted analysis could not be performed. Table 2 summarizes all the pooled results and respective sensitivity and subanalysis.

Early Seizures

Six RCTs and 11 nonrandomized studies evaluated early seizure incidence as a primary outcome with N = 8,413. The random-effects analysis showed an overall trend toward decreased seizure risk before 7 days post-TBI in the treatment group vs the comparator group (no ASM or placebo). Of 3,931, 84 (2.14%) had early seizures in the exposed group vs 203 of 4,482 (4.53%) in the unexposed group. In the pooled analysis, prophylaxis resulted in a significant difference in the risk for early seizures (risk ratio [RR] 0.43, 95% confidence interval [CI] 0.33–0.57, $p < 0.00001$, Figure 2A). Also, there was low heterogeneity across the studies ($I^2 = 3\%$, $p = 0.42$ for heterogeneity, Figure 2A). Among the RCTs, the pooled result was RR 0.36, 95% CI 0.21–0.61, $p = 0.0002$, $I^2 = 14\%$, $p = 0.33$ for heterogeneity (Figure 2A). Among the nonrandomized studies, the pooled result was RR 0.48, 95% CI 0.35–0.66, $p < 0.00001$, $I^2 = 0\%$, $p = 0.47$ for heterogeneity (Figure 2A).

We excluded 8 studies in the sensitivity analysis, considering only trials with low or moderate risk of bias or that included only patients with moderate to severe TBI. The random-effects analysis yielded similar results, with homogeneity among the studies (RR 0.33, 95% CI 0.21–0.51, $p < 0000001$, $I^2 = 0\%$, $p = 0.60$ for heterogeneity, Figure 2B).

Epilepsy or Late Seizures

Six RCTs and 6 nonrandomized studies evaluated epilepsy incidence as a primary outcome with N = 2,250. The random-effects analysis showed no significant benefit for ASM vs placebo or no ASM to prevent epilepsy after a TBI. One hundred sixty-two patients of 1,234 (13.1%) had epilepsy in the exposed group, and 137 of 1,016 (13.7%) had epilepsy in the unexposed group. In the pooled analysis, prophylaxis resulted in a nonsignificant difference in the risk for epilepsy (RR 0.79, 95% CI 0.47–1.33, $p = 0.38$, Figure 3A). There was considerable heterogeneity among the studies ($I^2 = 75\%$, $p < 0.00001$ for heterogeneity, Figure 3A).

Among the RCTs, the pooled result was RR 0.90, 95% CI 0.57–1.40, $p = 0.63$, $I^2 = 58\%$, $p = 0.04$ for heterogeneity (Figure 3A). Among the nonrandomized studies, the pooled result was RR 0.85, 95% CI 0.23–3.17, $p = 0.81$, $I^2 = 85\%$, $p < 0.00001$ for heterogeneity (Figure 3A). The duration of treatment varied from 5 days to 24 months among the included studies, but the length was fixed within the same study. The meta-regression statistics showed no significant association between the duration of treatment with ASMs and the log risk ratio for epilepsy incidence ($Z = 0.93$, 95% CI −0.000177 to 0.000496, $p = 0.35$) (eFigure 1A, links.lww.com/CPJ/A408). This meta-regression did not include

Table 1 Baseline Characteristics of the Included Studies

Study	Country	Population[a]	Follow-up/ duration of treatment	Intervention group		Control group	
				Outcomes[b]	Notes	Outcomes[b]	Notes
Randomized trials							
Glotzner et al., 1983[21]	DE	N = 151; >15 y of age; severe TBI; 88.5% male.	24 mo/24 mo	Carbamazepine Early seizure: 8/75 Epilepsy: 14/75 Mortality: 27/75	Participants were treated to reach serum levels of 300–600 μg. The first dose was given immediately after the accident (no dosage given).	Placebo Early seizure: 22/76 Epilepsy: 20/76 Mortality: 20/76	Details not provided
Mcqueen et al., 1983[22]	UK	N = 164; ages 5–65 y; severe TBI; 79% male (PHT); 80% male (PBO).	24 mo/12 mo	Phenytoin Epilepsy: 8/84	Child (5–15 y) 5 mg/kg; adults 300 mg During f/u, adjusted to achieve plasma concentration 40–80 μmol/L.	Placebo Epilepsy: 7/80	Matching placebo capsules
Pechadre et al., 1991[23]	FR	N = 86; ages 5–60 y; severe TBI; 80% male.	24 mo/12 mo	Phenytoin Early seizure: 2/34 Epilepsy: 2/34 Mortality: 2/34	10 mg/kg by slow IV pump 40 mg/min	Placebo Early seizure: 13/52 Epilepsy: 22/52 Mortality: 3/52	Matching placebo capsules
Pradhanang et al., 2019[24]	NP	N = 52; mean age 64.25 (±14.04) y; mild to severe TBI; 86.5% male.	6 mo/7 d	Phenytoin Early seizure: 0/25 Mortality: 0/25	IV loading dose of 17 mg/kg, added in 100 mL of 0.9% saline. Dose administration: 300 mg daily.	No ASM Early seizure: 3/27 Mortality: 3/27	Details not provided
Temkin et al., 1990[25]	US	N = 404; mean age 34 (±18) y; moderate to severe TBI; 78% male (PHT); 75% male (PBO)	24 mo/12 mo	Phenytoin Early seizure: 7/208 Epilepsy: 57/208 Mortality: 50/208	Initial dose 20 mg/kg IV within 24 h of injury Therapeutic dose: total 40–80 μmol/L, 10–20 mg/L Dose administration: daily dose varied based on the individual serum level: 200–1200 mg to maintain serum levels.	Placebo Early seizure: 26/196 Epilepsy: 41/196 Mortality: 42/196	PBO was given daily but was not more specified.
Temkin et al., 2007[26]	US	N = 499; mean age of 34.3 (±16.6) vs 34.4 (±17.88) y; moderate to severe TBI.	6 mo/5 d	High-dose MgSO4 (n = 59) Low-dose MgSO4 (n = 191) Early seizure: 1/250 Epilepsy: 15/249 Mortality: 42/233	High dose: 1.2–2.5 mmol/L, initial IV load of 0.425 mmol/kg over 15 min followed by continuous infusion (0.1 mmol/kg/h) to maintain the target range for 5 d. Therapeutic dose: 1.25–2.5 mmol/L Low dose: 1.0–1.85 mmol/L, initial IV load of 0.3 mmol/kg over 15 min followed by continuous infusion (0.05 mmol/kg/h) to maintain the target range for 5 d. Therapeutic dose: 1.0–1.85 mmol/L	Placebo 1 (n = 58) Placebo 2 (n = 190) Early seizure: 0/249 Epilepsy: 14/249 Mortality: 35/233	Normal saline 0.9%
Young et al., 1983 (1st report)[27]	US	N = 244; mean age 24.4 (±1.29) vs 25.8 ± (1.47) y, mild to severe TBI; 80.9% (PHE) males; 84.3% (PBO) males.	18 mo/7 d	Phenytoin Early seizure: 5/136 Mortality: 12/136	Initial dose: 11 mg/kg at 25 mg/min plus 13 mg/kg intramuscularly. If levels were adequate, 8.8 mg/kg was administered daily or adjusted as needed. Therapeutic dose: plasma concentrations 10–20 μg/mL.	Placebo Early seizure: 4/108 Mortality: 11/108	Identical IV phenytoin diluent (10% ethanol, propylene glycol 40%, and water 50%) or a placebo capsule
Young et al., 1983 (2nd report)[27]	US	N = 214; mean age of 25.2 y; mild to severe TBI.	18 mo/18 mo	Phenytoin Epilepsy: 13/105	Initial dose: 11 mg/kg at 25 mg/min plus 13 mg/kg intramuscularly. If levels were adequate, 8.8 mg/kg was administered daily or adjusted as needed. Therapeutic dose: plasma concentrations 10–20 μg/mL.	Placebo Epilepsy: 8/74	Identical IV of phenytoin diluent (10% ethanol, propylene glycol 40%, and water 50%) or a placebo capsule

Continued

Table 1 Baseline Characteristics of the Included Studies *(continued)*

Study	Country	Population[a]	Follow-up/ duration of treatment	Intervention group		Control group	
				Outcomes[b]	Notes	Outcomes[b]	Notes
Nonrandomized trials							
Bhullar et al., 2014[28]	US	N = 93; mean age 36 (±16) vs 41 (±18) y; mild to severe TBI; 65% males (PHT); 84% males (no AED).	Until the discharge (details not provided)/7 d	Phenytoin Early seizure: 1/50 Mortality: 4/50	Participants were treated to reach serum levels of 1–2 μg/mL. IV loading dose of 20 mg/kg (maximum, 2,000 mg). IV maintenance dose 5 mg/kg/d, every 8 h.	No ASM Early seizure: 2/43 Mortality: 3/43	Details not provided
Candy et al., 2019[29]	AU	N = 610; mean age 71 y; severe TBI; 58% males.	7 d/7 d	ASM Early seizure: 3/102	LEV in N = 93 (91%), PHT in N = 4 (4%), valproate in N = 2 (2%), and PHE loading followed by regular LEV in N = 3 (3%).	No ASM Early seizure: 18/580	Details not provided
Debenham, 1991[30]	CA	N = 1,008; mean age 52 (±22.3) y; mild to severe TBI.	7 d/7 d	Phenytoin Early seizure: 23/653	IV loading dose of 17 mg/kg over 30–60 min. IV or oral maintenance dose 300 mg/d.	No ASM Early seizure: 31/355	Details not provided
Formisano et al., 2007[31] (prospective)	IT	N = 82; mean age 25.5 y; severe TBI; 72% males.	24 mo/details not provided	ASM Epilepsy: 27/69	Phenobarbital in 58%, carbamazepine in 21.7%, PHT in 14.5%, and combined therapy in 5.8%.	No ASM Epilepsy: 0/13	Details not provided
Formisano et al., 2007[31] (retrospective)	IT	N = 55; mean age 27.1 y; severe TBI; 78% males.	24 mo/details not provided	ASM Epilepsy: 5/17	Carbamazepine in 58.9%, phenobarbital + carbamazepine in 17.6%, phenobarbital in 11.7%, PHE in 5.9%, clonazepam in 5.9%.	No ASM Epilepsy: 5/38	Details not provided
Inglet et al., 2016[32]	US	N = 2,111; median age 49 y; mild to severe TBI; 64.4% males.	Until the discharge (details not provided)/7 d	ASM Early seizure: 2/557 Mortality: 79/557	Phenytoin, fosphenytoin, valproic acid, phenobarbital, or levetiracetam.	No ASM Early seizure: 21/1,554 Mortality: 96/1,554	Details not provided
Khor et al., 2017[33]	US and CN	N = 522; median age 45 (29–59) y; mild to severe TBI; 75.9% male.	7 d/7 d	Levetiracetam Early seizure: 10/272	500 mg every 12 h for 7 d	No ASM Early seizure: 7/250	Details not provided
Klein et al., 2012[34]	US	N = 126; age 6–87 y, mild to severe TBI; 78.6% males.	24 mo/30 d	Levetiracetam Epilepsy: 6/66 Mortality: 5/46	PHE was initially administered IV 20 mg/kg for 1 wk after TBI. LEV 55 mg/kg/d was administered within 8 h after TBI, followed by 2 doses at 8 AM/8 PM for 30 d.	Placebo Epilepsy: 8/60 Mortality: 3/40	PBO was not specified. PHE was initially administered IV 20 mg/kg for 1 wk after TBI.
Lavergne et al., 2018[35]	CA	N = 120; mean age 72.4 y; CSDH due to a mild TBI; 73.3% males (AED); 78% males (no AED).	30 d/details not provided.	PHE or LEV Mortality: 1/30	Details not provided.	No ASM Mortality: 2/90	Details not provided
Liou et al., 2020[36]	TW	N = 276; mean age 42.4 (±23.8) y; mild to severe TBI; 57.5% males.	6 mo–8 mo/details not provided.	ASM Early seizures: 0/138 Epilepsy: 2/138 Mortality: 10/138	Details not provided.	No ASM Early seizures: 7/138 Epilepsy: 3/138 Mortality: 9/138	Details not provided

Continued

Table 1 Baseline Characteristics of the Included Studies *(continued)*

Study	Country	Population[a]	Follow-up/ duration of treatment	Intervention group		Control group	
				Outcomes[b]	Notes	Outcomes[b]	Notes
Ma et al., 2010[37]	CN	N = 159; 81.1% of participants were between 19 and 60 years old and had mild to severe TBI; 76.7% males.	7 d/7 d	Valproate Early seizure: 0/35	IV initial therapy at 10–15 mg/kg/d, followed by oral valproate products.	No ASM Early seizure: 7/124	Details not provided
Nichol et al., 2020[38]	CA	N = 96, mean age 48 (±6) vs 55 (±2) y; moderate to severe TBI; 63.5% males.	7 d/7 d	PHE or LEV Early seizure: 0/8	Details not provided.	No ASM Early seizure: 12/88	Details not provided
Ohimor et al., 1996[39]	US	N = 85; mean age 30.8 vs 31.4 y; moderate to severe TBI; 68.2% males.	30 d/7 d	Phenytoin Early seizure: 0/44	N = 20 received IV loading dose from 300 to 1,000 mg. N = 24 received no loading dose. Maintenance dose: 300 mg/d	No ASM Early seizure: 9/41	Details not provided
Rish et al., 1973[40]	US	N = 1,614; >18 y of age; mild to severe TBI.	7 d/7 d	ASM Early seizure: 18/1,136	ASM infusion within 6 h of injury. Diphenylhydantoin in 93% (300–400 mg/d). Phenobarbital in 4%. Combined therapy in 3%.	No ASM Early seizure: 17/465	Details not provided
Servit & Musil, 1981[41]	CZ	N = 167; mean age of 30.6 y; severe TBI; 76.6% males.	3 y–13 y/24 mo	PHE or phenobarbital Epilepsy: 3/143	Phenytoin 160–240 mg/d Phenobarbital 30–60 mg/d	No ASM Epilepsy: 6/24	Details not provided
Wohns & Wyler, 1979[42]	US	N = 62; mean age 29 (±19) y; severe TBI; 75.8% males.	6 mo–6 y/details not provided	Phenytoin Epilepsy: 5/50	Participants were treated to reach serum levels of 10–20 μg/mL. Therapeutic dose: 400 mg/d.	No ASM Epilepsy: 6/12	Details not provided
Zangbar et al., 2016[43]	US	N = 416; mean age of 47 (±23) vs 45 (±25) y, severe TBI; 66.6% males.	7 d/7 d	Levetiracetam Early seizure: 4/208	Details not provided.	No ASM Early seizure: 7/208	Details not provided

Abbreviations: ASM = antiseizure medication; AU = Australia; CA = Canada; CSDH = chronic subdural hematoma; CZ = Czech Republic; DE = Germany; FR = France; IT = Italy; LEV = levetiracetam; N = number of participants; NP = Nepal; NRCT = nonrandomized clinical trial; PHE = phenytoin; TBI = traumatic brain injury; TW = Taiwan; UK = United Kingdom; US = United States.
[a] Population: median or mean age in the treatment group vs median or mean age in the control group.
[b] Outcomes: number of seizure episodes/all participants of the treatment or control group.

Table 2 Summary of Pooled Findings (ASM vs Placebo or No ASM)

Outcome	Effect size	95% confidence interval	I^2, %	*p* Value
Effectiveness outcomes				
Early seizures (new onset until 7 d post-TBI)	0.43 (RR)	0.33–0.57	3	<0.00001
Early seizures: sensitivity analysis	0.33 (RR)	0.21–0.51	0	<0.00001
Epilepsy (new onset after 7 d post-TBI)	0.79 (RR)	0.47–1.33	75	0.38
Epilepsy: sensitivity analysis	0.84 (RR)	0.49–1.43	66	0.51
Epilepsy: subanalysis of studies within 18–24 mo of follow-up	1.01 (RR)	0.61–1.68	63	0.96
Safety outcome				
All-cause mortality	1.32 (RR)	1.00–1.75	43	0.05
All-cause mortality: sensitivity analysis	1.20 (RR)	0.95–1.51	0	0.13
All-cause mortality: subanalysis of studies within 18–24 mo of follow-up	1.16 (RR)	0.89–1.51	0	0.26

Abbreviations: ASM = antiseizure medication; RR = risk ratio; TBI = traumatic brain injury.

Formisano et al.[31] and Whons and Wyler[42] because they had not provided details about the duration of treatment with ASM.

We excluded 5 studies in the sensitivity analysis, considering only trials with low or moderate risk of bias or that included only patients with moderate to severe TBI. The random-effects analysis yielded similar results, with a substantial heterogeneity (RR 0.84, 95% CI 0.49–1.43, $p = 0.51$, $I^2 = 66\%$, $p = 0.02$ for heterogeneity, Figure 3B). The pooled analysis of 8 studies with a follow-up of 18–24 months also found a nonsignificant difference in the risk for epilepsy, with a substantial heterogeneity (RR 1.01, 95% CI 0.61–1.68, $p = 0.96$, $I^2 = 63\%$, $p = 0.008$ for heterogeneity, Figure 3C).

All-Cause Mortality

Six RCTs and 5 nonrandomized studies evaluated all-cause mortality incidence as a primary outcome with N = 4,089. The random-effects analysis showed a nonsignificant benefit in mortality risk when comparing the exposed (232 of 1,532; 15.1%) with the unexposed group (227 of 2,557; 8.9%). In the pooled analysis, prophylaxis increased the risk for all-cause mortality (RR 1.32, 95% CI 1.00–1.75, $p = 0.05$, Figure 4A). The heterogeneity was moderate ($I^2 = 43\%$, $p = 0.06$ for heterogeneity, Figure 4A).

Among the RCTs, the pooled result was RR 1.15, 95% CI 0.92–1.44, $p = 0.21$, $I^2 = 0\%$, $p = 0.66$, for heterogeneity (Figure 4A). Among the nonrandomized studies, the pooled result was RR 2.06, 95% CI 1.60–2.61, $p < 0.00001$, $I^2 = 0\%$, $p = 0.48$, for heterogeneity (Figure 4A). The duration of treatment varied from 5 days to 24 months among the included studies, but the length was fixed within the same study. The meta-regression statistics showed no significant association between the duration of treatment with ASMs and the log risk ratio for all-cause mortality ($Z = -0.49$, 95% CI −0.0003004 to 0.0001796, $p = 0.62$) (eFigure 1B, links.lww.com/CPJ/A408). This meta-regression did not include Lavergne et al. and Liou et al. trials because they had not provided details about the duration of treatment with ASM.[35,36]

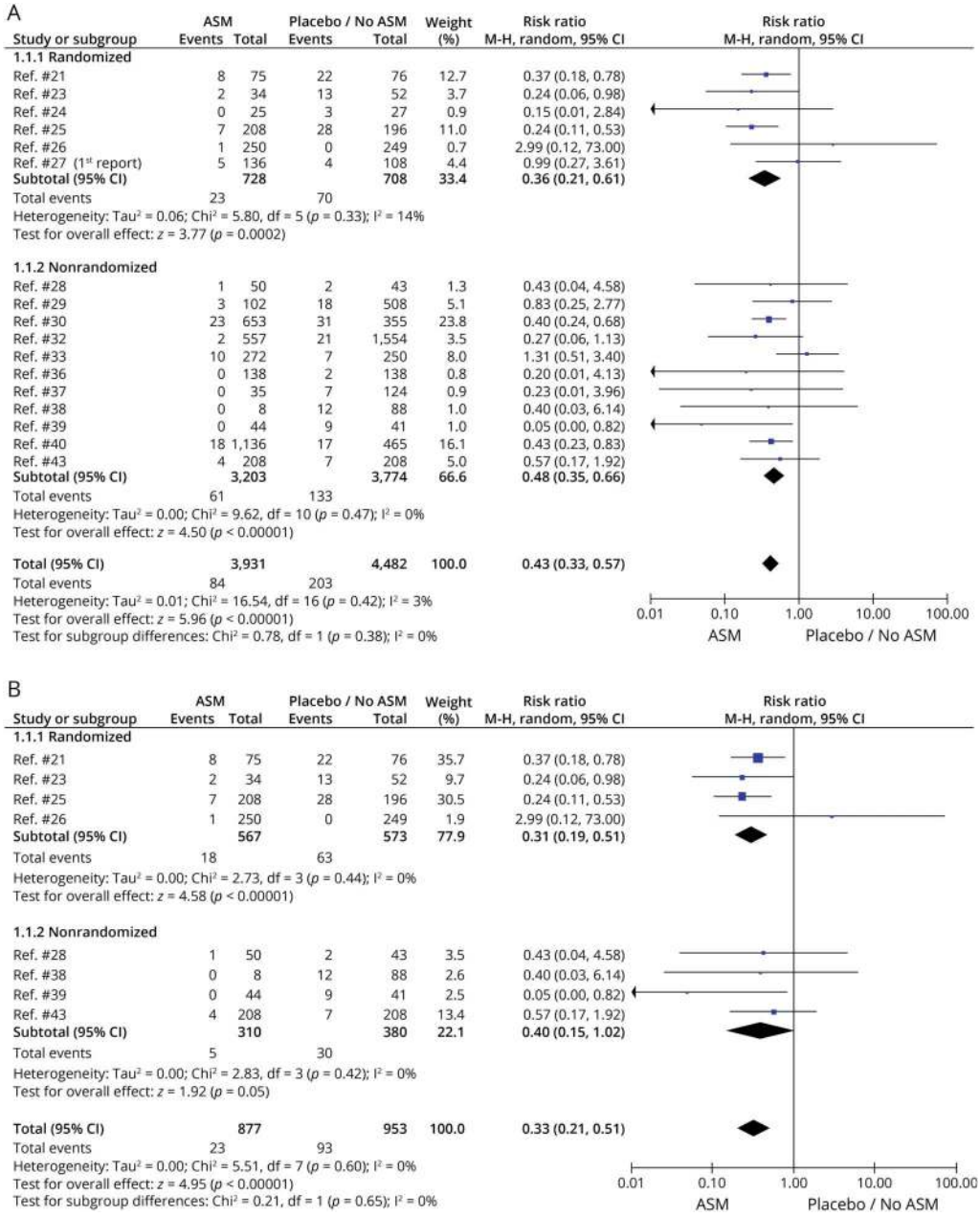
We excluded 6 studies in the sensitivity analysis, considering only trials with low or moderate risk of bias or that included only patients with moderate to severe TBI. All-cause mortality did not differ between the groups, with no observed heterogeneity (RR 1.20, 95% CI 0.95–1.51, $p = 0.13$, $I^2 = 0\%$, $p = 0.98$ for heterogeneity, Figure 4B). The pooled analysis of 8 studies with a follow-up of 18–24 months also found a nonsignificant difference in the risk for all-cause mortality, with no heterogeneity (RR 1.16, 95% CI 0.89–1.51, $p = 0.26$, $I^2 = 0\%$, $p = 0.89$ for heterogeneity, Figure 4C).

Risk-of-Bias Assessment

eFigure 2 (links.lww.com/CPJ/A408) reports the individual appraisal of each RCT. Despite the moderate risk of bias, RCTs are still maintained as high-quality studies. Of the 7 RCTs included, 4 failed to provide their randomization protocols.[21,23,25,27] One study presented significant baseline differences between exposed and nonexposed groups.[22] Three did not note blinding strategies of patients or investigators.[21,23,24]

eFigure 3 (links.lww.com/CPJ/A408) reports the individual appraisal of each nonrandomized study's risk of bias. We found 5 studies at serious risk of confounding bias due to a lack of study control measures.[29,31,40-42] Other 5 studies were at moderate risk of confounding bias due to important, uncontrollable confounding variables.[28,33,37-39] All nonrandomized studies showed a moderate risk of bias in the outcome assessment due to an unblinding.

Figure 2 Early Seizures in the Overall Study Population



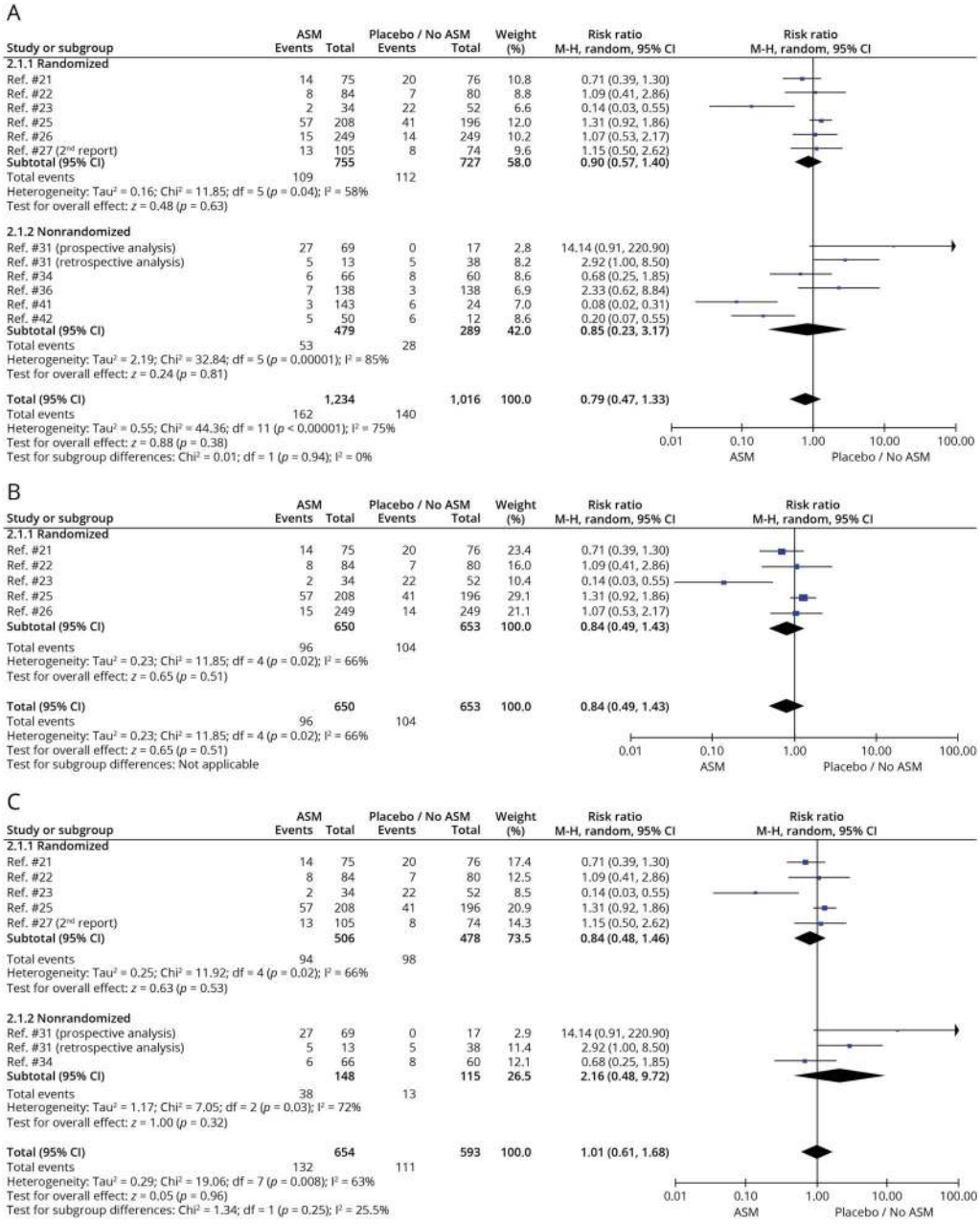
(A) A primary random-effect analysis comparing ASM use to placebo or no ASM (17 studies and n = 8,413). (B) Early seizure pooled results after sensitivity analysis (including only studies with moderate to severe TBI and excluding studies with serious risk of bias). Eight studies and n = 1,830. ASM = antiseizure medication; CI = confidence interval; df = degree of freedom; M-H = Mantel-Haenszel test.

On funnel plot analysis for the primary outcomes, studies occupied a slightly asymmetric distribution according to weight and converged toward the pooled effect as the weight increased (eFigure 4, links.lww.com/CPJ/A408). Therefore, there is no evidence of significant publication bias.

Evidence Quality Assessment

There is a high overall evidence quality assessment of that early primary ASM prophylaxis significantly lowers the early seizure incidence. For epilepsy/late seizure outcome, the overall evidence quality assessment was low for no significant effect of ASM prophylaxis due to substantial heterogeneity, serious risk of bias from some observational studies, and increased imprecision. Moreover, there is a moderate overall quality of evidence of no significant effect of early primary ASM prophylaxis on all-cause mortality risk due to increased risk of inconsistency and imprecision among observational studies. eTable 3 (links.lww.com/CPJ/A408) provides a summary of the GRADE quality ratings for all outcomes.

Figure 3 Epilepsy in the Overall Study Population



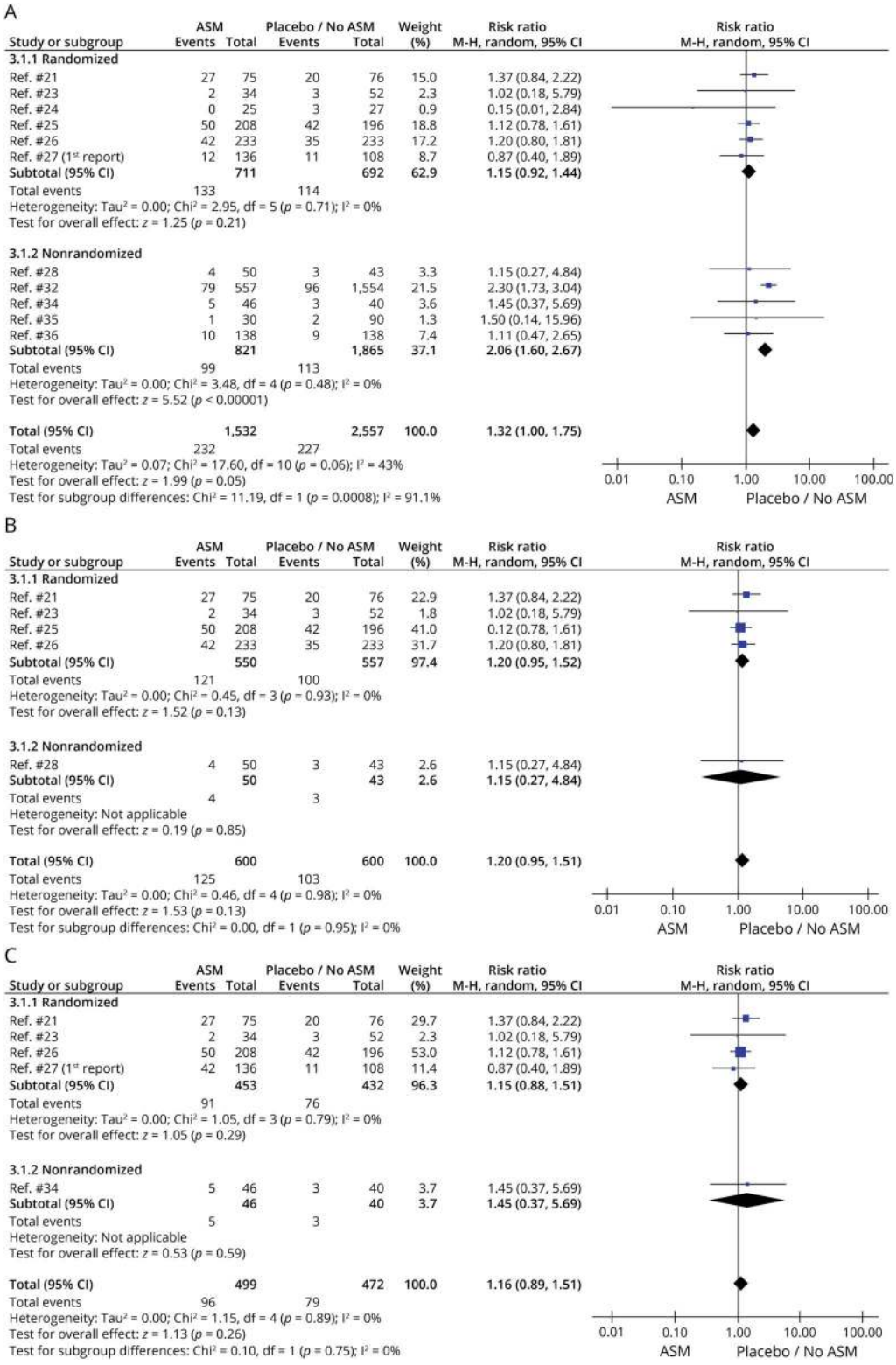
(A) A primary random-effect analysis comparing ASM use with placebo or no ASM (12 studies and n = 2,250). The study conducted by Formisano et al. [2007] was treated as two separate trials for the purpose of analysis. (B) Epilepsy pooled results after sensitivity analysis (including only studies with moderate to severe TBI and excluding studies with serious risk of bias). Five studies and n = 1,303. (C) Epilepsy pooled results after the subanalysis (including only studies with a follow-up duration of 18–24 months). Eight studies and n = 1,247. The study conducted by Formisano et al. [2007] was treated as 2 separate trials for the purpose of analysis. ASM = antiseizure medication; df = degree of freedom; M-H = Mantel-Haenszel test.

Discussion

The present study investigates the evidence of the association of early primary seizure prophylaxis with ASM and the 18- or 24-month epilepsy/late seizure risk or all-cause mortality in adults with new-onset TBI, in addition to early seizure risk. Within the limitations of included studies, the primary seizure prophylaxis within 7 days postinjury did not appear to be associated with a substantial difference in the 18- or 24-month epilepsy risk or all-cause mortality but showed high evidence of lower early seizure risk.

The Brain Trauma Foundation's guideline supports early antiseizure prophylaxis with phenytoin in TBI to minimize the risk of early seizures and consequent secondary brain injury.[10] Early posttraumatic seizures increase the risk for secondary brain injury and worse outcomes after a TBI due to intracranial hypertension and brain tissue hypoxia.[44] The

Figure 4 All-Cause Mortality in the Overall Study Population



(A) A primary random-effect analysis comparing ASM with placebo or no ASM (11 studies and n = 4,089). (B) All-cause mortality pooled results after sensitivity analysis (including only studies with moderate to severe TBI and excluding studies with serious risk of bias). Five studies and n = 1,200. (C) All-cause mortality pooled results after the subanalysis (including only studies with a follow-up duration of 18–24 months). Five studies and n = 971. ASM = antiseizure medication; CI = confidence interval; *df* = degree of freedom; M-H = Mantel-Haenszel test.

present careful analysis of the current literature showed that early ASM use was consistently associated with decreased risk of early seizure after TBI compared with placebo or no ASM groups.

Our results align with previous meta-analysis and current guidelines recommending early seizure prophylaxis while we add high-quality evidence in favor of ASM use to prevent early seizures.[10,12-14] Because we assume that mild cases are treated with no ASM in the included studies, we decided to make a sensitivity analysis excluding studies that included mild TBI cases. The favorable effect of ASMs on early seizure prophylaxis was still maintained after the sensitivity analysis, showing a substantial difference with no heterogeneity. However, while ASMs pose a risk of increased morbidity, they do not necessarily provide prophylaxis against epilepsy/late seizures or all-cause mortality.

Posttraumatic epilepsy (PTE) can have a significant negative effect on the patient's quality of life because it adds complexity to the existing consequences of TBI and challenges the reintegration into the community. The current guideline does not recommend the prophylactic use of ASM to specifically prevent posttraumatic late seizures/epilepsy because the evidence is unclear.[10] In the present study, we did not find a substantial beneficial effect of ASM prophylaxis on the risk for epilepsy in a pooled population of patients with TBI. Overall, the GRADE score was low, indicating considerable uncertainty in the estimated effects. If analyzing only the RCTs, the results give us a moderate quality of evidence regarding the lack of benefit association. However, it is uncertain whether the early use of ASM prevents epilepsy/late seizures owing to the low/very low quality of evidence from some nonrandomized data.

There was considerable heterogeneity among the included studies analyzing the PTE outcome. Potential reasons for heterogeneity include (1) differences in study design (randomized vs nonrandomized), (2) differences in injury severity across the included studies, and (3) differences in inclusion and exclusion criteria resulting in residual clinical and statistical heterogeneity, although these are felt to be minimal. After removing all nonrandomized studies in the sensitivity analysis, the heterogeneity decreased substantially. There continued to be a nonsignificant association between ASM prophylaxis and PTE development. For that reason, sensitivity analysis did not affect the results and showed a moderate quality of evidence.

Eight of 11 studies analyzing PTE development after a TBI had a fixed follow-up between 18 and 24 months (vs. others with much shorter or longer follow-ups). To limit heterogeneity, we decided to perform subanalysis including only studies with this follow-up duration. Primary seizure prophylaxis with ASM vs placebo or no such prophylaxis offered no difference in risk for post-TBI epilepsy during a follow-up of 18–24 months. In contrast, 2 studies with a longer follow-up duration showed a statistically significant decrease in epilepsy risk.[41,42] These findings, though, have not been consistently confirmed in other randomized and nonrandomized studies included in this study.

The different types of brain injury and the presence of comorbidities may also be related to the heterogeneity within each group. The type of brain injury (e.g., subdural hematoma, cortical contusion, and penetrating cranial lesion) or preexisting conditions (e.g., metabolic conditions) can significantly affect epilepsy development after brain trauma.[45,46] However, the included studies did not disclose patient-level information to draw any conclusions riding their effect on ASM prophylaxis on post-TBI epilepsy or mortality.

Meta-regression analyzing a possible association between epilepsy and the duration of treatment was performed to search for a potential source for heterogeneity. Also, we proposed that a long course of ASM could relate to a low risk of epilepsy. However, the meta-regression showed no association between them. Overall, increased heterogeneity and a slight asymmetry in funnel plots indicate that the state of the current evidence makes it challenging to draw a definitive conclusion, and further studies are necessary to solve this uncertainty.

We aimed to determine whether there is high-quality evidence on the effect of ASM prophylaxis on mortality. The present study reported a nonsignificant difference between the groups with moderate heterogeneity among the studies. Just 1 study showed a substantial result for the benefit of the unexposed group in mortality protection, yet it had a risk for detection bias by no blinding in outcome assessment.[32]

Two previous meta-analyses exploring post-TBI mortality are available in the literature. Thompson et al. looked to expand on the work of Schierhout et al., and both found no beneficial effect of prophylactic ASM on mortality.[16,47] However, they did not exclude studies containing previous or current ASM use from the unexposed group, such as Manaka and Szaflarski.[48,49] Thompson et al. also included Young et al. (2004), who analyzed the outcomes in a restricted pediatric population with an age range of 3.3–9.4 years.[16,50]

As high TBI severity is associated with more significant mortality, evaluating that only studies with moderate to severe cases showed much less heterogeneity among the studies, but still no significant difference between the groups.[51,52] In addition, meta-regression did not show an association between mortality and treatment duration with ASMs. Our subanalysis presented a nonsubstantial effect of ASM use on all-cause mortality risk in an 18- to 24-month follow-up. Through our assessment, the overall GRADE rating of the evidence quality for early ASM prophylaxis association with all-cause mortality risk was moderate, especially due to some included nonrandomized studies, that

explicitly presented a serious risk for bias. This meant that our confidence in this estimate was fairly limited, and the true safety may differ from the estimated safety. The RCTs however gave us a high strength of evidence regarding a nonsubstantial effect of early prophylaxis with ASM on all-cause mortality. The RCTs indeed presented high-level information even with some concerns regarding the randomization process such as no statement about participants/physicians blinding or the lack of allocation process description. The pooled data maintained the consistency, directness, and precision.

The strengths of this study include the extensive literature in our systematic review, comprising both nonrandomized and RCT studies without restrictions for the year of publication or language. We conducted a thorough analysis by extracting results from moderate to high quality studies and explored outcomes using sensitivity analysis, meta-regression, and investigation of publication bias. Additionally, we extensively explored potential sources of heterogeneity in this review. Our evaluation of the overall evidence quality using the GRADE system increases the strength of this study.

Our study has some limitations. First, there is a crucial gap in the literature considering the lack of new randomized clinical trials. Only 2 RCTs were published in the last 20 years.[24,26] Not unexpectedly, some old studies did not meet the current standard for research rigor. For example, the method of assigning cases to treatment was unclear, and the treatments were not blinded. Because of the small number of articles identified through the databases, it is possible that studies with relevant potential for the topic have not been identified by our search strategy in the literature.

Second, 16 of the 23 included studies were not randomized. A stratification by study design was performed to mitigate the effect of differential baseline prognosis between the exposure and no exposure and, consequently, provide insight to explain some contrasts with previously reported meta-analysis. Third, most of the included studies following previous meta-analysis have a moderate risk of bias in some critical domains, such as confounding control and reporting bias. We considered these potential biases when interpreting the findings of this review.

To perform the adjusted risk analysis using generic variance methods, the observational studies should report their effect measure with respective CI or SE calculated by regression models. These are generally preferable to analyze because they usually reduce the effect of confounding.[19] Because we had no observational study reporting their risk estimates using the RR and respective CI or SE for the outcomes, we could not perform the adjusted RR analysis, which limits our results.

Among the included studies providing absolute risks, the length of follow-up varied considerably. To minimize this heterogeneity, we performed subanalysis of studies with 18–24 months of follow-up. We must, however, interpret our findings with caution. Because the studies tended to have different lengths of follow-up, pooled absolute differences calculated using participants rather than person-years as denominators assume an equal length of follow-up across studies and can result in biased estimates of absolute risk differences.

The heterogeneous nature of the studies available in the literature is another limitation of this study. Previous meta-analysis reflected this heterogeneity, often showing I^2 more than 54%. Although we could address this to some extent through random-effect analysis, stratification by design, sensitivity analysis, and meta-regression, some concerns remain. The lack of patient-level data may have affected the ability to identify other sources of heterogeneity. Indeed, many clinical indicators of interest were not investigated, such as epidural and subdural hematoma, parenchymal contusions, penetrating brain injury, diffuse axonal injury, or comorbidities. The population evaluated across several included studies is male, young, and White, restraining the generalizability to people in minority subgroups, such as women, transgender people, elderly, Latin, African, or Native Americans. In the same way, most studies analyzed outcomes associated with older rather than newer ASMs.

Despite these limitations, our study offers a comprehensive summary of the evidence on ASM effect post-TBI that could be useful in guiding clinical practice and future research. New efforts

TAKE-HOME POINTS

- Posttraumatic antiseizure medication (ASM) prophylaxis has become the standard of care for minimizing brain damage, but its use could be associated with unfavorable outcomes.
- The current guideline recommends using ASM prophylaxis based on data from studies with selection bias or older-generation ASMs and may not be generalized to vulnerable subgroups at high risk for adverse outcomes (e.g., the older population).
- In this evidence quality assessment comprising 23 studies and 9,202 patients, primary seizure prophylaxis with ASM within 7 days posttraumatic brain injury (TBI) did not appear to be associated with a substantial difference in the 18- or 24-month epilepsy/late seizure risk or all-cause mortality when compared with alternative approaches (no ASM or placebo) among adults.
- The overall quality of evidence was low and moderate for epilepsy risk and all-cause mortality, respectively.

should investigate the possible sources of heterogeneity among the studies addressing the risk of epilepsy development, and new ASMs should be further explored. Therefore, improving the available data through newer, extensive, randomized clinical trials disclosing patient-level information is essential, in addition to the inclusion of underrepresented populations for better diversity, equity, and inclusion in health care.

This comprehensive review analyzes the association of early ASM prophylaxis with posttraumatic seizures and mortality. Our data suggest that the evidence showing no association between early ASM use and 18- or 24-month epilepsy risk in adults with new-onset TBI was of low quality. The analysis indicated a moderate quality for the evidence showing no effect on all-cause mortality. This requires further analysis to determine the prophylaxis' definitive validation in these contexts, especially addressing possible sources of heterogeneity and newer ASMs. Therefore, larger studies with higher methodological rigor are needed before making any recommendations, and future research efforts should investigate such associations through minority subgroups.

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