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Early Seizure Prophylaxis in Mild and Moderate Traumatic Brain Injury
A Systematic Review and Meta-Analysis

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IMPORTANCE Guidelines recommend seizure prophylaxis for early posttraumatic seizures (PTS) after severe traumatic brain injury (TBI). Use of antiseizure medications for early seizure prophylaxis after mild or moderate TBI remains controversial.

OBJECTIVE To determine the association between seizure prophylaxis and risk reduction for early PTS in mild and moderate TBI.

DATA SOURCES PubMed, Google Scholar, and Web of Science (January 1, 1991, to April 18, 2023) were systematically searched.

STUDY SELECTION Observational studies of adult patients presenting to trauma centers in high-income countries with mild (Glasgow Coma Scale [GCS], 13-15) and moderate (GCS, 9-12) TBI comparing rates of early PTS among patients with seizure prophylaxis with those without seizure prophylaxis.

DATA EXTRACTION AND SYNTHESIS The Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) reporting guidelines were used. Two authors independently reviewed all titles and abstracts, and 3 authors reviewed final studies for inclusion. A meta-analysis was performed using a random-effects model with absolute risk reduction.

MAIN OUTCOME MEASURES The main outcome was absolute risk reduction of early PTS, defined as seizures within 7 days of initial injury, in patients with mild or moderate TBI receiving seizure prophylaxis in the first week after injury. A secondary analysis was performed in patients with only mild TBI.

RESULTS A total of 64 full articles were reviewed after screening; 8 studies (including 5637 patients) were included for the mild and moderate TBI analysis, and 5 studies (including 3803 patients) were included for the mild TBI analysis. The absolute risk reduction of seizure prophylaxis for early PTS in mild to moderate TBI (GCS, 9-15) was 0.6% (95% CI, 0.1%-1.2%; $P = .02$). The absolute risk reduction for mild TBI alone was similar 0.6% (95% CI, 0.01%-1.2%; $P = .04$). The number needed to treat to prevent 1 seizure was 167 patients.

CONCLUSION AND RELEVANCE Seizure prophylaxis after mild and moderate TBI was associated with a small but statistically significant reduced risk of early posttraumatic seizures after mild and moderate TBI. The small absolute risk reduction and low prevalence of early seizures should be weighed against potential acute risks of antiseizure medications as well as the risk of inappropriate continuation beyond 7 days.

Supplemental content

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Traumatic brain injury (TBI) is one of the leading causes of death and disability worldwide.[1,2] Posttraumatic seizures (PTS) contribute to secondary brain damage after TBI and are associated with increased hospital length of stay, mortality, and worse functional outcomes.[3-5] PTS are divided into early, occurring within 7 days of trauma, and late, occurring after 7 days. Early and late PTS are distinct entities with different biological bases. TBI triggers early PTS and occurs in up to 15% or more of patients with severe TBI, defined as a postresuscitation Glasgow Coma Scale (GCS) score of 8 or less.[6-10] Randomized clinical studies, meta-analyses, and current guidelines support the use of seizure prophylaxis for the prevention of early PTS in severe TBI.[10-12] Rates of early PTS in severe TBI are less than 5% with seizure prophylaxis.[10,13,14]

Late PTS, also known as posttraumatic epilepsy, are considered unprovoked and are common. After severe TBI, late PTS occur in one-third of survivors of TBI, whereas mild TBI triples the risk of epilepsy compared with the general population.[8,13,15] Although seizure prophylaxis is effective in preventing early PTS, it is not effective in preventing late PTS.[14,16]

Early PTS are associated with an increased risk for late PTS, although it is unclear if this relationship is correlative or causative.[13,17-19] Like late PTS, early PTS are associated with markers of injury severity, positive computed tomography (CT) head findings, and temporal lobe trauma.[13,17,20] Although not well studied, no evidence supports that treating early PTS reduces the risk for late PTS. The majority of practitioners treat early PTS with antiseizure medications, limiting the ability to study this question.[21,22]

The rates of early PTS in mild (GCS, 13-15 with or without a positive CT head) or moderate (GCS, 9-12) TBI are much lower compared with those of severe TBI.[4,23] In both groups, rates of early PTS range from 0% to 4% in the reported literature, with most studies reporting rates less than 2%.[4,20,23-26] Although rates of late PTS are higher in moderate TBI compared with mild TBI, multiple studies have reported similar rates of early PTS for mild and moderate TBI.[4,23,24] This may reflect the low rates of early PTS overall and that moderate TBI is less common, accounting for 5% to 10% of TBI. A recent study with over 15 000 patients across the TBI severity spectrum did not find an increased risk for early PTS in moderate TBI compared with mild TBI.[4]

The effectiveness of seizure prophylaxis in mild (GCS, 13-15 with or without a positive CT head) or moderate (GCS, 9-12) TBI is unknown.[27-30] Despite this, many patients with mild and moderate TBI receive seizure prophylaxis, with at least one-quarter or more of patients inappropriately continuing antiseizure medication treatment past the 7-day prophylaxis window.[31,32] Significant variation exists in seizure prophylaxis prescriptions, which often vary across practitioners within the same hospital.[28] No major guidelines exist, to our knowledge, regarding seizure prophylaxis in mild TBI. This may reflect a lack of high-quality studies evaluating the effectiveness of seizure prophylaxis in early PTS or that no major neurology or epilepsy society has guidelines for management of posttraumatic epilepsy.[21] Despite this lack of guidance, clinicians must make thousands of decisions every day regarding seizure prophylaxis, as 80% of TBI is characterized as mild, and 1 million mild TBIs occur yearly in North America.[33,34]

Key Points

Question Is seizure prophylaxis associated with reduced risk for early posttraumatic seizures, defined as seizures within 7 days of injury, for patients with mild or moderate traumatic brain injury?

Findings In this systematic review and meta-analysis including 8 studies, the absolute risk reduction of seizure prophylaxis for early posttraumatic seizures was 0.6% in mild and moderate traumatic brain injury. The overall rate of early posttraumatic seizures was low, ranging from 0% to 4%.

Meaning Study results suggest that seizure prophylaxis was associated with a small, albeit significant, reduced risk for early posttraumatic seizures for mild to moderate traumatic brain injury; the small absolute risk reduction should be weighed against the risks of prescribing antiseizure medications.

Because of this practice variation, unknown effectiveness, and large potential for clinical impact, we sought to determine through a quantitative meta-analysis the association between seizure prophylaxis and risk reduction for early PTS in patients with mild and moderate TBI presenting to trauma centers in high-income countries.

Methods

We performed a systematic review and meta-analyses using accepted evidence-based techniques and followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) reporting guidelines (eMethods in Supplement 1).[35] Our protocol was registered with PROSPERO.[36]

Systematic Review

Our goal was to find studies that compared the effectiveness of seizure prophylaxis for early PTS with those who did not receive seizure prophylaxis. We searched PubMed, Google Scholar, and Web of Science for relevant articles published in English from January 1, 1990, through April 18, 2023. We searched using the following terms: traumatic brain injury, posttraumatic seizure, posttraumatic epilepsy, trauma and anticonvulsants, and prophylactic anticonvulsants. Additionally, we searched citations and reviews related to PTS.[11,37,38] Two investigators (M.P. and A.M.) independently screened all titles and abstracts. We downloaded relevant on-topic articles for review by 3 investigators (M.P., A.M., N.B.) for final inclusion.

Study Selection and Data Extraction

We included studies that compared seizure prophylaxis in early PTS to a control group after mild (GCS, 13-15) or moderate (GCS, 9-12) TBI. We defined seizure prophylaxis as any antiseizure medicine. Exclusion criteria included the following: (1) age younger than 18 years, (2) no comparator/control group without prophylaxis, (3) stratifying TBI severity by alternative severity scales such as the Abbreviated Injury Scale, (4) failure to report the rates of early PTS within 7 days, (5) patients with

preexisting seizure disorders, and (6) from World Bank designated low- or middle-income countries.[39]

To help limit heterogeneity between studies, our search was limited to studies of patients who presented to trauma centers in high-income countries. In the US and other high-income countries, trauma centers treat the vast majority of TBIs and are widely available.[40] Over 90% of the US population lives within 1 hour of a level 1 or 2 trauma center. Similarly, we limited our searches to studies from high-income countries due to the large differences in care for TBI and seizures in low- and middle-income countries. In low- and middle-income countries, trauma centers are less widely available, resulting in significantly more morbidity and mortality.[41] Monitoring and treatment for seizures is similarly different, with 75% of patients with epilepsy not receiving treatment in low-income regions and 50% not receiving treatment in middle-income countries.[41]

To ensure consistency, we excluded studies that did not include the entire 7-day period for early PTS. For example, some studies excluded seizures occurring during the first 24 hours after trauma (ie, immediate seizure) from analysis.[42] The first 24 hours after injury is the most common time to have an early PTS and may be a period where prophylaxis is most effective.[10,43]

A priori, our plan was to include patient-level data. Unfortunately, the large majority of studies were unable to share data because contact emails were no longer active, data were not available, or groups were unwilling to share data.[20,25,26,30,31,43,44] Due to our difficulty getting patient-level data, we decided to only include studies that reported data stratified by trauma severity using Glasgow Coma Scale (GCS) or were willing to share that that data with us.[24,45]

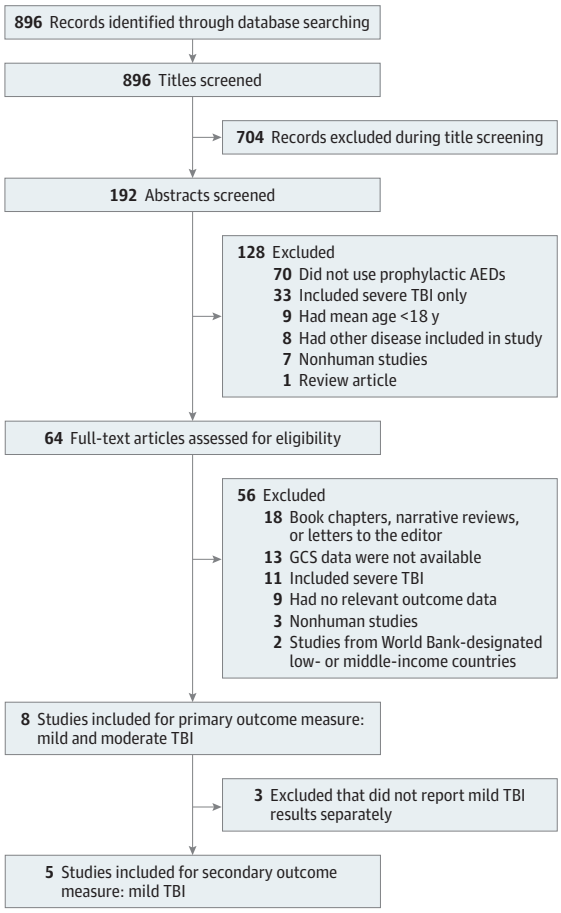
For included studies, we extracted publication year, country, and clinical data on early PTS. Patient race and ethnicity data were not formatted in articles in a fashion usable for analysis. When possible, we extracted mild and moderate data separately. Two investigators (M.P. and A.M.) independently extracted data and resolved discrepancies collaboratively.

Study Quality Assessment

We assessed the quality of the nonrandomized, observational studies using the Newcastle-Ottawa Scale (NOS), which is an easy to use, Cochrane-recognized quality checklist. The NOS contains 8 items categorized into 3 domains: selection (4 items), comparability (2 items), and outcome (3 items).[46,47] For the comparability section, we considered injury severity to be the most important factor. Additional important factors include age, mechanisms of injury, and additional injuries. For adequacy of follow-up, we considered studies with greater than 70% follow-up to be adequate.

Study quality was semiquantitatively assessed based on a star system, so that the highest quality of studies can receive up to 9 stars. Overall risk of bias was graded using the threshold for converting the NOS rating to Agency for Healthcare Research and Quality standards into good quality (7-9 points), fair quality (5-7 points), and poor quality. The NOS was assessed by 2 independent reviewers (M.P. and A.M.) for each study.

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Flow Diagram



AED indicates antiepileptic drug; GCS, Glasgow Coma Scale; TBI, traumatic brain injury.

Statistical Analysis

We used the metafor package, version 3.8,[48] in R, version 4.2 (R Project for Statistical Computing). For each study, we calculated the absolute risk reduction (ARR) and 95% CIs of seizure prophylaxis for early PTS in patients with mild and moderate TBI. We used a random-effects model to account for between-study heterogeneity. Due to the rarity of early PTS, many studies had no reported incidence of early PTS; therefore, we used ARR. As a secondary analysis, we repeated the meta-analysis using only mild TBI. We tested between-study heterogeneity using I^2 and Cochran Q test. We visually evaluated publication bias with funnel plots. Significance was defined as a 2-sided P value < .05.

Results

Literature Search

A systematic search of the literature yielded 896 studies, of which we reviewed 64 full articles after screening (**Figure 1**). We included 8 studies for the mild and moderate TBI

Table 1. List of Included Studies and Patient Characteristics[a]

Study	Type	Severity	Mild, %	AEDs used	Seizure prophylaxis			No seizure prophylaxis		
					PTS	No PTS	%	PTS	No PTS	%
Inglet et al,[25] 2016[b]	Retrospective	Mild-mod	89	Any	1	393	0.3	14	1372	1
Hazama et al,[26] 2018[b]	Retrospective	Mild-mod	86	Lev	0	158	0	2	139	1
Candy et al,[44] 2019[b]	Retrospective	Mild-mod	100	Any	1	44	2	13	437	3
Faropoulos et al,[20] 2020	Prospective	Moderate	0	Lev	13	416	3	21	421	5
DJohn et al,[31] 2020	Retrospective	Mild-mod	NA	Lev	6	147	4	0	250	0
Pingue et al,[24] 2021	Retrospective	Mild-mod	40	Any	1	51	2	7	167	4
Liou et al,[45] 2020[b]	Retrospective	Mild-mod	92	Any	0	171	0	6	1037	0.6
Pease et al,[28] 2022[b]	Prospective	Mild	100	Any	1	138	0.7	6	204	3
Total	NA	NA	NA	NA	23	1518	NA	69	4027	NA

Abbreviations: AED, antiepileptic drug; Lev, levetiracetam; mod, moderate; NA, not applicable; PTS, posttraumatic seizure; TBI traumatic brain injury.

[a] When possible, we tried to extract mild and moderate TBI data separately. Pease et al[28] and Faropoulos et al[20] only included mild and moderate TBI, respectively. DJohn et al[31] grouped mild and moderate TBI into 1 category called nonsevere, and thus, we could not determine the distribution of mild vs moderate TBI. Candy et al[44] dichotomized TBI into mild and nonmild, and we similarly could not include any moderate TBI in this study.

[b] Indicates that this study was also used in the mild TBI analysis.

Table 2. Evidence Grading With the Newcastle-Ottawa Scale (NOS)[a]

Study	Selection	Comparability	Outcome	Total points	Quality
Inglet et al,[25] 2016	4	2	2	8	Good
Hazama et al,[26] 2018	4	2	2	8	Good
Candy et al,[44] 2019	3	2	2	7	Good
Faropoulos et al,[20] 2020	4	2	2	8	Good
DJohn et al,[31] 2020	4	1	2	7	Good
Pingue et al,[24] 2021	3	2	3	8	Good
Liou et al,[45] 2020	4	2	2	8	Good
Pease et al,[28] 2022	4	2	2	8	Good

[a] We graded the 8 studies included in the meta-analysis. NOS categories (selection, comparability, outcome) are each divided into the respective subcategories. Overall quality of bias ranges between good quality (7-9 points), fair quality (5-7 points), and poor quality (0-2 points).

analysis[20,24-26,28,31,44,45] and 5 studies for the mild TBI analysis.[25,26,28,44,45] Studies were removed for being narrative (18 studies), not using GCS to stratify TBI severity (13 studies), not separating mild or moderate TBI from severe TBI (11 studies), early PTS outcome data not reported (9 studies), nonhuman studies (3 studies), and patients from middle- or low-income countries (2 studies). **Table 1** lists the studies included and individual study data. Although we did not complete a quantitative analysis of excluded articles, the rates of early PTS were similar, typically less than 4%.[4,23,29,30]

One-half of the studies reported patients with mild and moderate TBI separately.[24-26,45] Most studies, except for 2,[20,24] had significantly more (>80%) mild TBI than moderate (Table 1). Pingue et al[24] did not have any patients in the mild TBI group who received seizure prophylaxis. As a result, all patients with mild and moderate TBI were included in the mild and moderate analysis, but this study was not included in the mild TBI analysis because there was no comparison group (ie, there were only patients without seizure prophylaxis and mild TBI). Pease et al[28] and Faroloupos et al[20] included only mild or moderate TBI, respectively. DJohn et al[31] did not separate out mild and moderate TBI and was included in the mild and moderate analysis but not mild-only analysis.[31] Candy et al[44] dichotomized patients into mild TBI and nonmild TBI, and only patients with mild TBI were included. eTable 1 in Supplement 1 lists the distribution of patients with mild and moderate TBI.

Evidence Grading

All of the studies were cohort studies. Two[20,28] were prospective and the remainder retrospective. Overall, all the studies were graded as good quality on the NOS (**Table 2**). Common reasons for decreased quality were only including patients at rehabilitation hospitals[24] and failure to provide adequate follow-up information[20,25,26,31,44,45] or descriptions of patients lost to follow-up.[28]

Meta-Analysis Results

Overall, we included 8 studies[20,24-26,28,31,44,45] with 5637 patients. Of these, 1541 received seizure prophylaxis. We did not restrict based on type of antiseizure medication used for prophylaxis. Most patients were given levetiracetam, phenytoin, or valproic acid, depending on the study. Three studies only used levetiracetam for prophylaxis.[20,26,31]

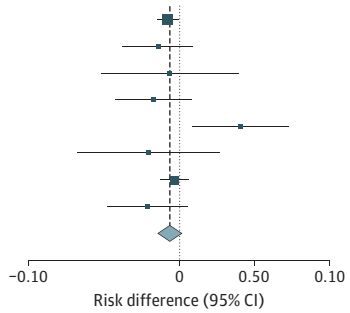
The included studies had diverse patient populations. The studies had a wide range of average age (33-65 years), radiographic injuries, and mechanism of injuries. Consistent with other studies in TBI, most of the patients were male. eTable 2 in Supplement 1 lists clinical information for individual studies. Due to inconsistent reporting of clinical information between studies, we did not perform further analysis of these data.

For studies of patients with mild and moderate TBI, the ARR with prophylaxis in early PTS was 0.6% (95% CI, 0.1%-1.2%; P = .02) (**Figure 2**). The rates of early PTS ranged from

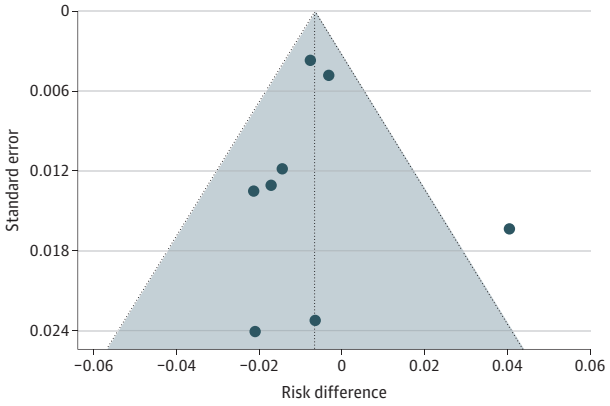
Figure 2. Absolute Risk Reduction for Seizure Prophylaxis in Mild and Moderate Traumatic Brain Injury (TBI)

A Absolute risk reduction for seizure prophylaxis in mild and moderate TBI

Source	Risk difference (95% CI)
Inglet et al,[25] 2016	−0.01 (−0.02 to 0)
Hazama et al,[26] 2018	−0.01 (−0.04 to 0.01)
Candy et al,[44] 2019	−0.01 (−0.05 to 0.04)
Faropoulos et al,[20] 2020	−0.02 (−0.04 to 0.01)
DJohn et al,[31] 2020	0.04 (0.01 to 0.07)
Pingue et al,[24] 2021	−0.02 (−0.07 to 0.03)
Liou et al,[45] 2020	0 (−0.01 to 0.01)
Pease et al,[28] 2022	−0.02 (−0.05 to 0.01)
Summary	−0.01 (−0.01 to 0)



B Funnel plot



A, Plot for mild and moderate TBI analysis. B, Funnel plot for mild and moderate TBI analysis.

0% to 4%, depending on the study. The number needed to treat to prevent 1 seizure was 167 patients. There was little heterogeneity with a negative Cochran *Q* test (P = .13) and an I^2 of 4%. Visually, there was minimal risk of publication bias on the funnel plot. One included study[31] was an outlier with a negative effect of seizure prophylaxis. Of note, this was the only study at a level 2 trauma center; the rest of the studies were at level 1 centers.[49]

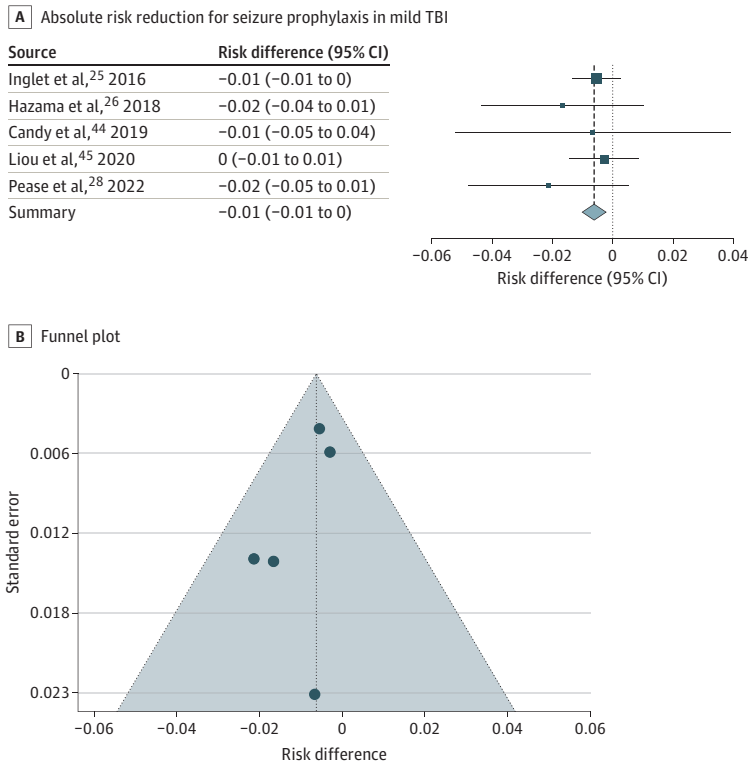
When only including mild TBI (5 studies, 3803 patients), the ARR of seizure prophylaxis for early PTS was also 0.6% (95% CI, 0.01%-1.2%; P = .04) (**Figure 3**). There was a similar amount of heterogeneity with a negative Cochran *Q* test (P = .71), and I^2 was insignificant. Visual analysis of the funnel plot showed minimal risk of publication bias.

Discussion

We performed a quantitative meta-analysis of the effectiveness of seizure prophylaxis for early posttraumatic seizures in patients with mild and moderate TBI presenting to trauma centers in high-income countries. We found an ARR of 0.6% for populations of both composite mild and moderate TBI as well as in cohorts with exclusively mild TBI. Our study showed a modest but clear trend toward the benefits of seizure prophylaxis in 8 studies,[20,24-26,28,31,44,45] which included a total of 5637 patients. Nonsevere TBI is very common; mild TBI alone affects over 1 million people yearly in North America yearly.[50] Although randomized clinical trials support the use of seizure prophylaxis in severe TBI, there are no individual studies demonstrating significant efficacy of seizure prophylaxis in mild or moderate TBI.[10] Neurotrauma practitioners routinely prescribe antiseizure medications for seizure prophylaxis despite lacking clear clinical evidence or supporting guidelines. Results of this meta-analysis suggest modest effectiveness of seizure prophylaxis in mild to moderate (GCS, 9-15) and mild (GCS, 13-15) TBI.

The ARR of seizure prophylaxis in early PTS was small: only 0.6%. By comparison, seizure prophylaxis reduces the risk of early PTS by almost 11% after severe TBI.[10] PTS are less common, both in the short and long term, after mild and moderate TBI compared with severe TBI.[13,17,51] Early PTS occur between 0% to 4% after mild TBI, which may in part explain the smaller absolute effect of seizure prophylaxis compared with severe TBI.[25,26,28,29,31,44,45] Despite lower ARR in mild and moderate TBI, early seizures may have a clinically significant effect in populations with mild and moderate TBI. Early seizures may incur longer hospitalizations, non-home discharge, prolonged use of antiseizure medications, unnecessary advanced diagnostic testing, as well as driving and work restrictions. Reducing seizure burden improves functional outcomes and quality of life in critically ill patients.[52]

Figure 3. Absolute Risk Reduction for Seizure Prophylaxis in Mild Traumatic Brain Injury (TBI)



A, Plot for mild TBI analysis. B, Funnel plot for mild TBI analysis.

Although this meta-analysis did show a modest yet clear associated risk reduction of early seizures using prophylaxis with antiseizure medications in mild and moderate TBI, the relatively small ARR coupled with the low incidence of PTS in these populations makes the decision to use seizure prophylaxis in nonsevere TBI challenging. We encourage practitioners to carefully weigh the prevalence and risks of early seizures against potential adverse events from antiseizure medications. Older antiseizure medications are associated with increased risks of hyponatremia, memory problems, and fatigue.[53-55] The depressive adverse effects of antiseizure medications on the central nervous system are felt more acutely by older adults, who make up the majority of those with mild TBI.[56,57] However, newer antiseizure medications such as levetiracetam may pose less risks. Up to one-quarter of patients are inappropriately discharged with antiseizure medications after failure to stop prophylactic medications after 7 days.[24,31] Prolonged and unnecessary antiseizure medication usage may also inhibit recovery from TBI, especially in moderate and severe TBI.[24] Practitioners should weight these costs with the potential benefits, listed previously, while considering the small ARR.

Although the effect is small overall for all patients with mild and moderate TBI, there may be a subset of patients for whom early seizure prophylaxis is more effective. Early PTS are associated with markers of injury severity and in particular, positive head CT findings including subdural hematomas and traumatic subarachnoid hemorrhage.[4] Temporal lobe contusions, in particular, predispose to PTS in both the short and long term.[17] For patients with risk factors for early PTS as described previously, treating clinicians should consider instituting seizure prophylaxis.

We grouped patients with mild and moderate TBI together in our main analysis. Although rates of posttraumatic epilepsy (ie, late PTS) are nearly 5 times higher after moderate compared with mild TBI,[8] several recent reports failed to find significant differences for early PTS.[4,24] Our mild TBI secondary analysis found the same effect size as the combined group, although the majority of patients had mild TBI. We did not complete an analysis with moderate TBI only, as moderate TBI accounted for roughly one-quarter of the patients, and separate data were often not reported.

Limitations

One of the major limitations of our study is the bias from retrospective studies of seizure incidence. Six of 8 studies were retrospective,[24-26,31,44,45] and only 1 prospective study used a validated questionnaire to record PTS.[28] Despite this, our studies were of higher quality when assessed with the NOS, a validated measure of cohort studies. Seven of 8 studies had a positive, albeit not significant, effect of seizure prophylaxis.[20,24-26,28,44,45] The only study with a negative effect was at a level 2 trauma center.[31] Patients with more severe injuries may be transferred to level 1 centers, limiting the generalizability of our findings.

None of our studies included randomized clinical trials, likely due to the rarity of early PTS in mild and moderate TBI. With a small effect size (0.6%), small risk of early PTS (0%-4%), and poor follow-up in mild TBI clinics (approximately 70%), a properly

powered clinical trial would require at least 10 000 patients, which would be challenging to complete.

The lack of randomized clinical studies may have introduced bias. In most included studies, individual practitioners decided whether to prescribe seizure prophylaxis. Many practitioners, both in general and in the studies included in our meta-analysis, tailor their approach—only prescribing seizure prophylaxis to those with more severe injuries.[25,26,45] In these cases, the bias from nonrandomization would work against the effectiveness of seizure prophylaxis, as the patients receiving medical prophylaxis are at higher risk for early PTS based on the individualized judgment made by the practitioner. Despite this negative bias, we found a positive effect for seizure prophylaxis in mild and moderate TBI.

We excluded 1 study[43] with a null effect that did not include patients who had seizures during the first 24 hours after trauma. The first day after trauma is the most common time for early PTS, with at least two-thirds of early PTS occurring during the first 24 hours.[10,58] Delaying treatment past the initial hospital entry may miss an opportunity for effective prophylaxis.

Conclusions

Results of this systematic review and meta-analysis of cohort studies suggest that seizure prophylaxis may be effective for preventing early PTS for mild and moderate TBI, with an absolute risk reduction of 0.6%. Practitioners should weigh low prevalence of early PTS and low risk reduction against risks of antiseizure medicine, including inappropriate long-term continuation.

ARTICLE INFORMATION

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Author Contributions: Dr Pease had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: Pease, González-Martínez, Castellano, Barot.
Acquisition, analysis, or interpretation of data: Pease, Mittal, Merkaj, Okonkwo, González-Martínez, Elmer, Liou, Pingue, Hammond, Abramovici.
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Critical review of the manuscript for important intellectual content: Pease, Mittal, Okonkwo, González-Martínez, Elmer, Liou, Hammond, Abramovici, Castellano, Barot.
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Administrative, technical, or material support: Pease, González-Martínez, Elmer, Hammond.
Supervision: Pease, Elmer, Pingue, Castellano, Barot.

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Data Sharing Statement: See Supplement 2.

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