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Systematic Review

The Impact of Levetiracetam versus Phenytoin as Second-Line Therapy for Status Epilepticus in the Emergency Department: A Systematic Review

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Abstract

Background: After benzodiazepine failure, status epilepticus (SE), a neurological emergency, necessitates immediate second-line treatment. Levetiracetam and phenytoin are commonly used, However, there is ongoing discussion over their relative safety and effectiveness in the emergency department (ED). **Objective:** to thoroughly examine the safety and efficacy of intravenous levetiracetam against phenytoin as a second-line treatment for SE in the ED that is benzodiazepine-refractory. **Methods:** The PRISMA 2020 standards were followed in conducting a systematic review. We looked for papers (within the previous five years) comparing the two medicines in ED patients with SE in PubMed/MEDLINE, Scopus, and Web of Science. Efficacy outcomes were seizure cessation rate, time to cessation, and 24-hour recurrence. Safety outcomes included adverse events. The Cochrane RoB 2 and ROBINS-I tools were used to evaluate the risk of bias. **Results:** Five studies (three RCTs, one quasi-experimental, one retrospective cohort; total n=523), all in pediatric populations, were included. Results indicated comparable efficacy for initial seizure cessation, with rates ranging from 78.8% to 94% for levetiracetam and 74.3% to 90.5% for phenytoin. According to two trials, levetiracetam considerably shortened the time it took for seizures to stop. Recurrence rates within 24 hours showed no significant difference. Safety data were insufficiently reported, but qualitative findings favored levetiracetam's tolerability. considerable variability, open-label designs, and

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a considerable risk of bias in non-randomized trials reduced the overall strength of the evidence. **Conclusion:** Levetiracetam and phenytoin demonstrate similar efficacy for aborting benzodiazepine-refractory SE in the ED. The choice between them may be guided by levetiracetam's potential for faster administration, more favorable pharmacokinetics, and superior safety profile, consistent with findings from larger pragmatic trials. Higher-quality, standardized research is needed to strengthen these conclusions.

Keywords: Status Epilepticus; Levetiracetam; Phenytoin; Second-Line Therapy; Emergency Department; Systematic Review; Seizure Cessation; Pediatric.

Introduction

With a high morbidity and mortality rate, status epilepticus (SE) is one of the most serious neurological crises seen in clinical practice. Operational thresholds are usually set at continuous seizure activity exceeding 5 minutes or recurrent seizures without a return to baseline. It is defined as a condition that arises either from the failure of the mechanisms responsible for seizure termination or from the initiation of mechanisms that lead to abnormally prolonged seizures. [1]. This medical emergency requires rapid, sequential pharmacological intervention to halt neuronal excitation, prevent irreversible neuronal injury, and mitigate systemic complications such as hyperthermia, acidosis, and cardiorespiratory compromise. The timely and effective management of SE is therefore a paramount concern for emergency physicians, neurologists, and intensivists alike.

The established treatment paradigm for convulsive SE follows a staged approach, with intravenous benzodiazepines—namely lorazepam, due to its quick start of action and great effectiveness in stopping seizures, diazepam and midazolam are often recommended as the first-line treatment.

[2]. However, a substantial proportion of patients, estimated between 30% to 40%, prove refractory to this initial intervention, necessitating prompt escalation to a second-line antiepileptic drug (AED) [3]. There has been discussion and development surrounding the choice of this second-line agent for a long time. Due to decades of clinical usage and recommendations from guidelines, intravenous phenytoin (or its prodrug fosphenytoin) has traditionally been the mainstay of second-line therapy [4]. Neuronal membrane stabilization is achieved by its use-dependent blockage of voltage-gated sodium channels. However, a troublesome pharmacokinetic profile that includes non-linear metabolism, substantial drug-drug interactions, and a known risk of severe side effects limits its usefulness. These include infrequent but severe skin responses, local tissue damage from extravasation (particularly "purple glove syndrome"), and cardiovascular instability (hypotension, bradycardia, arrhythmias) [5].

In recent years, intravenous levetiracetam has emerged as a compelling alternative for second-line SE management. Being a new modulator of synaptic vesicle protein 2A (SV2A) with a unique mechanism, it offers several theoretical and practical advantages in the emergency setting. These include a more favorable pharmacokinetic profile (linear metabolism, minimal protein binding, lack of hepatic enzyme induction/inhibition), the ability to administer a rapid intravenous bolus over 5 minutes, and an excellent acute safety and tolerability record with minimal cardiorespiratory effects [6]. Consequently, its use has increased dramatically, and it has been incorporated into

numerous institutional protocols. However, solid and consistent evidence showing that it is either superior to or not inferior than phenytoin in terms of seizure cessation effectiveness has been hard to come across, despite its appealing safety and user-friendly profile. At the core of contemporary SE management algorithms is the crucial question of these two agents' relative efficacy.

Existing evidence is characterized by heterogeneity and conflicting results. Although a number of meta-analyses and randomized controlled studies have determined that levetiracetam and phenytoin are equally effective in controlling seizures [7], other studies, particularly in specific subpopulations like children, have suggested potential differences in outcomes such as time to seizure termination or recurrence rates [8]. This lack of consensus creates uncertainty for clinicians at the bedside of a seizing patient. A synthesized, up-to-date analysis focusing specifically on their performance in the high-stakes environment of the emergency department is therefore urgently needed. In order to provide a concise, evidence-based summary that will guide clinical decision-making and protocol development, this systematic review attempts to compile the existing comparative literature on intravenous levetiracetam versus phenytoin as second-line therapy for benzodiazepine-refractory status epilepticus in the emergency department.

Methodology

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement was followed in the conduct and reporting of this systematic review[9].

Search Strategy and Information Sources

To find all relevant published research, a thorough electronic literature search was conducted. To make sure the review represented the most recent research and best practices, the search was limited to publications released in the last five years. For the past five years, the following electronic bibliographic databases were thoroughly searched: Web of Science Core Collection, Scopus, and PubMed/MEDLINE. Medical Subject Headings (MeSH) terms and free-text keywords pertaining to the population ("status epilepticus," "SE," "convulsive status"), the interventions ("levetiracetam," "Keppra," "phenytoin," "fosphenytoin," "Dilantin"), and the context ("emergency department," "ED," "emergency service") were all used in the search strategy. Boolean operators (AND, OR) were used to combine search phrases, and each database's syntax was modified accordingly. At first, there were no linguistic limitations. To find any more acceptable papers, the reference lists of all included research and pertinent review articles were carefully examined.

Eligibility Criteria and Study Selection

According to predetermined PICOS criteria, studies were chosen. Patients of any age who presented with convulsive or non-convulsive status epilepticus in an emergency room setting made up the population (P). Intravenous levetiracetam vs intravenous phenytoin (or fosphenytoin) as second-line therapy when first benzodiazepine treatment failed was the intervention and comparison (I/C). In addition to safety outcomes, the outcomes (O) included effectiveness indicators such seizure cessation rate, time to seizure cessation, and seizure recurrence within 24 hours. Randomized controlled trials (RCTs), quasi-experimental research, and prospective or retrospective observational cohort studies were the study designs (S) taken into consideration. Exclusion criteria included reviews, editorials, case reports, series with less than 10 patients, and studies that did not

directly compare or that did not take place in an emergency room.

The Rayyan online program for systematic reviews was used to oversee the study selection procedure [11]. All found records were uploaded into Rayyan when the database searches were completed, and duplicate citations were eliminated both electronically and manually. Two reviewers separately carried out the screening in two stages. Initially, abstracts and titles were checked against the qualifying requirements. Second, the whole texts of publications that could be of interest were obtained and carefully evaluated before being included. Disagreements between the two reviewers were settled at both phases by dialogue or, if required, third-party arbitration. The rationale behind the exclusion of research at the full-text stage was recorded.

Data Extraction and Data Items

In Microsoft Excel, a standardized and pilot-tested data extraction form was created. Two reviewers independently extracted data from each included study, and disagreements were settled by consensus. (1) Study characteristics: first author, publication year, journal, study location, study design, length, and sample size were among the retrieved data. (2) Participant attributes include baseline demographics, age range, and inclusion and exclusion criteria. (3) Details of the intervention: particular medication, dose, and method of administration for the groups receiving phenytoin and levetiracetam. (4) In addition to main and secondary effectiveness outcomes as indicated in each study, outcome data includes all reported safety and adverse event data (e.g., % with seizure cessation, mean time to cessation, recurrence rate). (5) The study's authors' main conclusions. Although it wasn't always possible, efforts were made to find supplemental materials or get in touch with the associated authors for studies where important information was missing from the primary text or abstract.

Risk of Bias Assessment in Individual Studies

As advised by the Cochrane Collaboration, each included study's risk of bias was thoroughly evaluated using instruments relevant to its design [10]. The updated Cochrane Risk of Bias instrument (RoB 2) was used for randomized controlled trials. Bias in the randomization process, bias resulting from deviations from intended interventions, bias resulting from missing outcome data, bias in outcome assessment, and bias in selecting the reported result are the five areas in which this test assesses bias. Each trial's total risk of bias was determined by assigning a risk rating of "Low," "Some concerns," or "High" to each area. The Risk Of Bias In Non-randomized research - of Interventions (ROBINS-I) tool was utilized for non-randomized research (quasi-experimental and cohort studies). An overall assessment of "Low," "Moderate," "Serious," or "Critical" risk of bias is the result of this tool's assessment of bias across seven domains: confounding, participant selection, intervention classification, deviations from interventions, missing data, outcome measurement, and selection of reported results. Two reviewers independently completed each evaluation, and differences were settled by discussion.

Data Synthesis

Because the included studies showed considerable clinical and methodological variability, including differences in patient age groups (e.g., pediatric-only vs. mixed populations), exact definitions of seizure cessation and status epilepticus, medication dosage schedules, and research methodologies (observational vs. RCTs)—a quantitative synthesis

(meta-analysis) was judged unsuitable. As a result, a narrative synthesis of the findings is provided, centered on the important outcomes of safety and efficacy.

Results:

The PRISMA flowchart describes the research selection procedure used in the systematic review. 261 entries were found in the first database search. After 144 duplicate entries were eliminated, 117 unique records were screened for titles and abstracts, which led to the elimination of 79. Thirty-one reports were left for a thorough eligibility review after the entire texts of 38 papers were attempted to be retrieved, seven of which were not available. 26 reports were disqualified after full-text assessment for the following reasons: Five were conference papers without fully available data, ten researched the incorrect population, and eleven did not disclose the proper conclusion. As a result, five papers in all satisfied all inclusion requirements and were added to the final systematic review.

The included studies, which are included in Table 1, use a variety of approaches to examine how well levetiracetam and phenytoin work together as second-line treatments for juvenile status epilepticus in emergency situations. The research consists of three randomized controlled trials (RCTs) [12, 15, 16], one quasi-experimental study [13], and one retrospective cohort analysis [14], are carried out in pediatric inpatient or emergency rooms. The studies' overall sample sizes ranged from 41 to 185 individuals. With patient ages ranging from one month to 18 years. All studies explicitly focused on children presenting with convulsive status epilepticus (CSE) or benzodiazepine-refractory seizures, confirming that the patient population is pertinent to the main inquiry of the review. The discovered literature mostly focuses on South Asia, with some research coming from Pakistan [12, 13, 15].

The efficacy and safety outcomes extracted from these studies are presented in Table 2, revealing a complex picture with no clear, unanimous superior agent. In terms of initial seizure cessation, two RCTs reported higher success rates for levetiracetam (94% vs. 77% [15] and 91.4% vs. 74.3% [12]), while one RCT [16] and the retrospective study [14] found nearly equivalent rates between the two drugs. The time to cessation of seizures, where reported, favored levetiracetam, demonstrating a significantly faster resolution in two studies [13, 15]. Regarding seizure recurrence within 24 hours, the available data shows no significant difference between the treatments. The study by Zaman et al. [13] revealed recurrence rates of 11.1% for phenytoin and 15.6% for levetiracetam, whereas Kartek et al. [16] found rates of 35% and 38.1%, respectively.

Notable inconsistencies and limitations in outcome reporting across the studies complicate direct comparison and synthesis. Critical data, such as standardized times for assessing primary seizure cessation, detailed adverse event profiles, and specific criteria for "seizure control," were frequently not reported (marked as NM in Table 2). For instance, while some studies defined cessation within 5 minutes [16] or 30 minutes [15] post-infusion, others did not specify the time window [12, 14]. Furthermore, the safety profile, a key differentiator given phenytoin's known risks of cardiac arrhythmias and extravasation injury, was not quantitatively detailed in any of the abstract-provided results, though one study [15] qualitatively noted levetiracetam had a better safety profile.

Significant limitations across the body of evidence are shown by the risk of bias evaluation, which is described in Table 3. The trials that were

randomized [12, 15, 16] were all conducted in an open-label fashion, introducing performance and detection bias, with one RCT [16] deemed to have a high risk of bias overall. The research that are not randomized [13, 14] were evaluated using the ROBINS-I tool and were determined to have a significant overall risk of bias, mainly because of basic confounding problems arising from their retrospective and quasi-experimental designs, where it is challenging to assign results exclusively to the intervention due to the lack of randomization. As a result, even if these studies offer insightful clinical information, the overwhelming body of data with some reservations about the high/serious risk of bias means that the results of this systematic review should be regarded with extreme caution.

Discussion

While leveti.e.racetam demonstrates a trend towards faster seizure cessation and a potentially superior safety profile, phenytoin remains a comparably effective agent in terms of initial seizure termination and prevention of short-term recurrence. The central finding of comparable efficacy between the two drugs is consistent with several pivotal high-quality trials conducted in adult and mixed populations. Levetiracetam, fosphenytoin, and valproate were directly compared in patients aged 2 years and older in the seminal Established Status Epilepticus Treatment experiment (ESETT), a double-blind, randomized controlled experiment. Without supplementary anticonvulsant medication, it found no meaningful difference in the primary endpoint of better responsiveness at 60 minutes and the absence of clinically obvious seizures. The efficacy was 47% for levetiracetam, 45% for fosphenytoin, and 46% for valproate [17]. This rigorous multicenter trial provides strong evidence of therapeutic equivalence among second-line agents, directly supporting the non-inferiority findings observed in studies like Kartek et al. [16] and Köle et al. [14] within our review. Levetiracetam and phenytoin were also compared in a large pragmatic trial in the United Kingdom called the Convulsive Status Epilepticus in Children Trial (ConSEPT); the primary outcome of clinical cessation of seizures at 5 minutes did not show any significant difference (68% for levetiracetam vs. 60% for phenytoin; risk difference 7.4%). [18] These large-scale studies effectively contextualize the conflicting efficacy rates (e.g., 91.4% vs. 74.3% in Arshad et al. [12]) from smaller, single-center studies within our review, suggesting that such dramatic differences may be attributable to smaller sample sizes, varying definitions of seizure cessation, or unmeasured confounding factors rather than a true large effect size.

However, when moving beyond the binary outcome of initial seizure cessation, a more distinct profile for levetiracetam emerges, particularly regarding safety and practical administration. Phenytoin, and its prodrug fosphenytoin, carry well-documented risks of severe adverse effects, including cardiac arrhythmias (e.g., hypotension, bradycardia), venous irritation and purple glove syndrome, and complex pharmacokinetics requiring careful infusion and monitoring [19]. In contrast, levetiracetam has a notably benign acute safety profile, can be administered as a rapid intravenous bolus over 5 minutes, and lacks significant drug interactions or cardiovascular effects [20]. This practical advantage is critically important in the chaotic environment of the emergency department. While our included abstracts did not provide detailed quantitative safety data, the qualitative conclusion from Naeem et al. [15] that levetiracetam has "fewer and less severe side effects" aligns perfectly with the established pharmacologic literature.

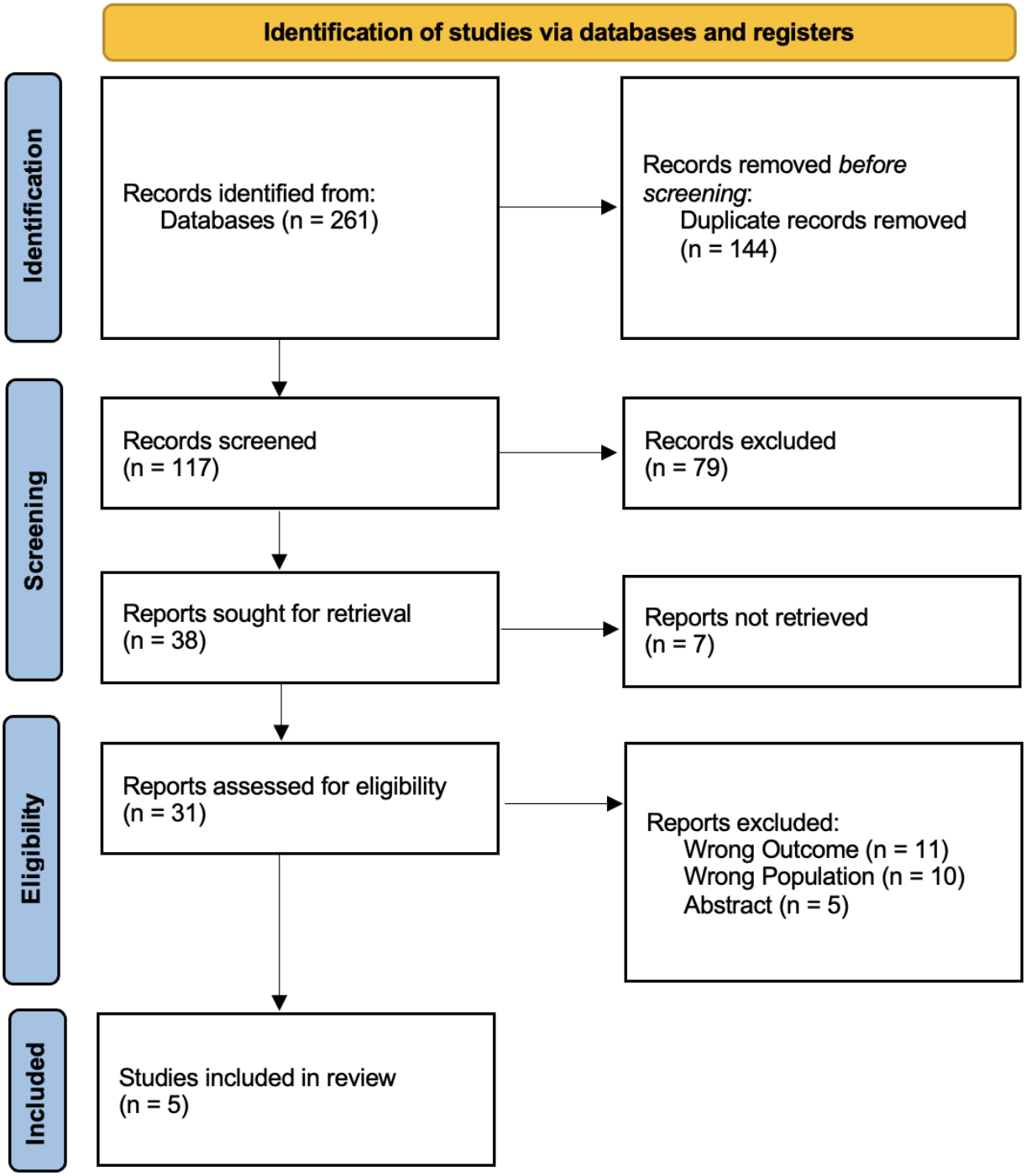

Figure (1): PRISMA Flowchart of Study Selection Process

Table 1: Demographic and Study Characteristics

Study (Author, Year, Reference)	Study Location	Study Design	Study Duration	Total Sample Size	Levetiracetam Group (n)	Phenytoin Group (n)	Age Range	Key Inclusion Criteria
Anjum et al., 2024 [12]	Pediatric Emergency Department of Children Hospital, Faisalabad, Pakistan	Randomized Controlled Trial	August 2022 to January 2023 (6 months)	70	35	35	NM	Pediatric status epilepticus patients in emergency department
Zaman et al., 2022 [13]	Department of Pediatric Medicine, Combined Military Hospital, Kharian, Pakistan	Quasi-experimental study	January to December 2020	90	45	45	NM	Children with status epilepticus in emergency department
Köle et al., 2022 [14]	NM	Retrospective study	NM	185	85	100	1 month to 18 years	Children with acute seizures or convulsive status epilepticus repetitive seizures receiving second-line antiepileptic drug
Naeem et al., 2023 [15]	NM	Randomized Controlled Trial	NM	137	NM	NM	NM	Children with benzodiazepine-refractory status epilepticus
Kartek et al., 2024 [16]	Pediatric Emergency (NM)	Prospective, randomized controlled, open-label study	NM	41	20	21	3 months to 15 years	Children with status epilepticus in pediatric emergency

Table 2: Efficacy and Safety Outcomes

Study (Author, Year, Reference)	Seizure Cessation Rate (Levetiracetam)	Seizure Cessation Rate (Phenytoin)	Time to Seizure Cessation (Levetiracetam)	Time to Seizure Cessation (Phenytoin)	Recurrence within 24h (Levetiracetam)	Recurrence within 24h (Phenytoin)	Adverse Events
Anjum et al., 2024 [12]	91.4% (32/35)	74.3% (26/35)	NM	NM	NM	NM	NM
Zaman et al., 2022 [13]	NM	NM	16.40 ± 4.50 seconds	22.24 ± 3.85 seconds	15.6% (7/45)	11.1% (5/45)	NM
Köle et al., 2022 [14]	78.8%	84%	NM	NM	NM	NM	NM
Naeem et al., 2023 [15]	94%	77%	19.94 ± 3.76 minutes	23.791 ± 9.1 minutes	NM	NM	NM
Kartek et al., 2024 [16]	85% (17/20)	90.5% (19/21)	NM	NM	35% (7/20)	38.1% (8/21)	NM

Table 3: Risk of Bias Assessment for All Included Studies

Study (Author, Year)	Study Design	Tool Used	Domain 1: Randomization /Confounding	Domain 2: Selection of Participants	Domain 3: Classification of Interventions	Domain 4: Deviations from Intended Interventions	Domain 5: Missing Data	Domain 6: Measurement of Outcomes	Domain 7: Selection of Reported Result	Overall Risk of Bias

Randomized Controlled Trials		**Cochrane RoB 2**								
Anjum et al., 2024 [12]	RCT	RoB 2	Low	–	–	Some Concerns	Low	Some Concerns	Low	**Some Concerns**
Naeem et al., 2023 [15]	RCT	RoB 2	Low	–	–	Some Concerns	Low	Some Concerns	Low	**Some Concerns**
Kartek et al., 2024 [16]	Open-label RCT	RoB 2	Low	–	–	**High**	Low	**High**	Low	**High**
Non-Randomized Studies		**ROBINS-I**								
Zaman et al., 2022 [13]	Quasi-experimental	ROBINS-I	Serious	Moderate	Low	Serious	Low	Low	Low	**Serious**
Köle et al., 2022 [14]	Retrospective Cohort	ROBINS-I	Serious	Moderate	Low	Low	Low	Low	Low	**Serious**

This safety differential was a key factor in the design and findings of the EcLiPSE trial, Levetiracetam and phenytoin were tested in a multicenter RCT conducted in the UK for children with convulsive status epilepticus. As for main effectiveness, it likewise revealed no difference (72% seizure cessation with levetiracetam vs. 76% with phenytoin), it highlighted the safety and ease-of-use advantage of levetiracetam [21]. The faster time to seizure cessation reported by Zaman et al. [13] (16.40 vs. 22.24 seconds) and Naeem et al. [15] (19.94 vs. 23.79 minutes) in our review, though from studies with methodological limitations, further supports the logistical argument for levetiracetam, as faster administration and action can streamline emergency care.

The focus of this review on pediatric populations is particularly salient, as treatment choices must consider developmental pharmacology and long-term neurocognitive impacts. The evidence from dedicated pediatric trials like ConSEPT [18] and EcLiPSE [21] has been instrumental in informing pediatric-specific protocols. Levetiracetam and phenytoin are just as effective as second-line medications for children with convulsive status epilepticus who do not respond to first-line benzodiazepine therapy, according to a meta-analysis by Lyttle et al. that included data from ConSEPT and EcLiPSE [22]. This high-level synthesis directly corroborates the overall message from our collected studies. Furthermore, the potential for phenytoin to induce enzyme-altering effects and its non-linear pharmacokinetics pose greater challenges in children, who may have variable metabolic rates and comorbid conditions. The retrospective finding by Köle et al. [14] that an age of less than 36 months was a significant risk factor for seizure recurrence underscores the importance of age-specific considerations, though it does not differentiate between drug responses. The move towards levetiracetam in many pediatric protocols is thus driven not by overwhelming evidence of superior efficacy, but by the convergence of equivalent efficacy, a superior safety margin, and greater administrative simplicity, reducing the potential for iatrogenic harm during a high-stakes emergency.

Limitations

The substantial limitations of the main research examined inevitably restrict the results of this evaluation. According to the risk of bias evaluation, the body of evidence consists of research with **some concerns** to **high/serious risk of bias**. The predominant issues include the open-label design of the RCTs [12, 15, 16], This poses a significant danger of confounding in non-randomized research, as well as a high chance of performance and detection bias [13, 14] due to their quasi-experimental and retrospective designs. Furthermore, there is substantial clinical and methodological heterogeneity: definitions of status epilepticus and seizure cessation vary, dosing protocols differ (e.g., 20 mg/kg vs. other doses), follow-up durations are inconsistent, and safety outcomes are poorly and inconsistently reported. The small sample sizes of several studies limit their statistical power to detect anything but very large differences in efficacy or to reliably identify less common adverse events. The geographic focus of research in South Asia may potentially restrict the findings' applicability to other healthcare environments with varying clinical procedures and resource availability. The results should be seen as generating hypotheses for more thorough inquiry rather than offering conclusive counsel because of these limitations, which also hinder a comprehensive meta-analysis.

Conclusion

The two agents have largely similar efficacy for the critical outcomes of initial seizure cessation and 24-hour recurrence prevention. The most consistent differentiating factors are not in efficacy, but in the domains of safety, pharmacokinetics, and ease of use, which strongly favor levetiracetam. This aligns with the current paradigm shift in clinical practice, as reflected in recent guidelines from organizations like the Neurocritical Care Society, which now list levetiracetam, valproate, and fosphenytoin as equally acceptable second-line options, with the choice often guided by side-effect profile and specific patient factors. The findings from large, rigorous trials provide a robust external framework that validates and strengthens the collective message from the smaller studies reviewed here. In order to further optimize management strategies for this potentially fatal neurological emergency in both pediatric and adult populations, future research should concentrate on prospectively evaluating standardized protocols that incorporate levetiracetam as a preferred second-line agent, with accurate outcome measurement and thorough safety reporting.

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