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Levetiracetam versus phenytoin for the treatment of established status epilepticus: A systematic review and meta-analysis of randomized controlled trials

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Key Points

Both levetiracetam and phenytoin were effective in controlling seizure activity for established status epilepticus

Levetiracetam was not significantly superior to phenytoin in seizure cessation.

Levetiracetam was not superior to phenytoin in mortality, serious adverse events, or other adverse events.

Abstract:

Objectives: To compare the efficacy and safety of levetiracetam and phenytoin for the treatment of established status epilepticus

Methods： In this systematic review, we searched Medline, Embase, and Cochrane databases from their inception with no language restrictions until May 8, 2019, for randomized controlled trials comparing the efficacy and safety of levetiracetam and phenytoin for the treatment of established status epilepticus. A meta-analysis was conducted to calculate the risk ratio (RR) using random-effects models.

Results: We identified six trials with a total of 765 participants. Levetiracetam was not associated with an increased rate of clinical seizure cessation within 15 min compared with phenytoin (RR, 1.03; 95%CI, 0.92-1.16; I^2=23%; levetiracetam, 65.1 % [241/370] vs phenytoin, 64.3 % [222/345];19 more events [95% CI, -51 to 103] per 1000 participants; moderate-quality evidence). The sample size met the optimum size in trial sequential analysis. There were also no statistically significant effects on all-cause mortality (RR, 0.88; 95% CI, 0.40-1.97; I^2=0%), serious adverse events (RR, 0.51; 95% CI, 0.19-1.36; I^2=0%), or any adverse events (RR, 0.95; 95% CI, 0.67-1.34; I^2=0%).

Conclusions: Medium-quality evidence suggested that levetiracetam was not significantly superior to phenytoin in seizure cessation in patients with established status epilepticus.

KEYWORDS： Status epilepticus, Levetiracetam, Phenytoin, Meta-analysis

1 Introduction

Convulsive status epilepticus is the second most common neurologic emergency, with an annual incidence of 10–40 cases per 100,000 people.[1, 2] Morbidity and mortality are considerable, and thus, timely termination of convulsive status epilepticus is the primary goal of management.[3-5] Benzodiazepines, typically lorazepam or diazepam, are used as first-line therapy for status epilepticus.[6-8] However, benzodiazepines fail to terminate convulsive status epilepticus in about 40–60% of patients. The neurocritical care society guideline recommend phenytoin, levetiracetam, or valproate for the treatment of benzodiazepine-refractory status epilepticus, also known as established status epilepticus. [Brophy et al 2012] Yet, only fosphenytoin (a precursor drug to phenytoin) is approved by the Food and Drug Administration (FDA) for this indication in adults, with no second-line treatments approved for children. [6-8] Further, evidence for this indication is sparse. Most evidence for phenytoin came from RCTs where phenytoin was administered as a second-line drug irrespective of whether status epilepticus was controlled by benzodiazepines; the studies did not demonstrate benzodiazepine-refractory status epilepticus.

Levetiracetam, a newer anticonvulsant, has been viewed as a potential alternative to phenytoin for the treatment of established status epilepticus.[2] Levetiracetam can be given more rapidly by intravenous infusion (5 min) than phenytoin (20 min).[10] In observational studies, levetiracetam was superior to phenytoin in higher seizure cessation rates [11] and less serious adverse events[12] for the treatment of established status epilepticus. However, data from randomized controlled trials conducted so far does not support the use of one drug over another.[13, 32, 33] A systematic review and meta-analysis of two small trials did not find a statistically significant difference between levetiracetam and phenytoin, likely due to the limited sample size.[14]

Since the publication of that review, several trials[15-18] on this topic have become available, resulting in a combined sample size that is 5 times greater than the previous meta-analysis. Therefore, we performed a systematic review and meta-analysis to compare the efficacy and safety of levetiracetam versus phenytoin as the treatment of established status epilepticus. We also performed trial sequential analyses to identify if firm evidence is reached in cumulative studies.

2 MATERIALS AND METHODS

2.1 Protocol and guidance

This study protocol and hypotheses is registered on the Open Science Framework (https://osf.io/b3zjn). The systematic review was conducted following the recommendations of The Cochrane Handbook for Systematic Reviews of Interventions[19] and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[20] The PRISMA checklist is presented in Supplement eTable 1. Ethical approval was not obtained because this is a systematic review.

2.2 Eligibility criteria

Inclusion criteria following PICOS (population, interventions, comparators, outcomes, and study design):

(1) Population: The population of interest included patients with convulsive status epilepticus

(generalized or focal) despite first-line antiepileptic drugs (e.g., benzodiazepines) . Status epilepticus was defined as convulsive seizures lasting >5 minutes.

(2) Intervention: Intravenous levetiracetam.

(3) Comparison: Intravenous phenytoin (fosphenytoin in the USA)

(4) Outcome: The primary outcome was clinical seizure cessation within 15 min. Secondary outcomes were all-cause mortality, admission to critical care, and good functional outcome.

(5) Study design: Randomized controlled trials

Exclusion Criteria: Types of myoclonic, absence, or non-convulsive status epilepticus.

2.3 Data Sources

We searched the databases Medline (from 1956 to May 8, 2019), Embase (from 1976 to May 8, 2019), and Cochrane databases (from 1992 to May 8, 2019) . We also checked the reference lists of previous reviews for additional studies. We searched trial registries on ClinicalTrials.gov for ongoing studies or the availability of completed studies. We did not use any language restrictions. Details of the search strategy used for each database are reported in Supplement eTable 2.

2.4 Study selection

After removal of duplicates, two authors (YZ and LJ) independently screened the title and abstracts of the search results. The full text of the remaining papers was assessed independently by the two authors. Disagreements between the two authors were resolved by a third reviewer

(FF).

2.5 Data collection process

Two authors (YZ and YF) independently extracted data on study characteristics and event rates from the eligible trials into standardized collection forms. The following baseline characteristics were extracted from the included studies: key study characteristics (e.g., first author, year of publication, study design, country in which the study was performed and number of cite, study period, number of included patients, sex, age, initial dosages) and quantitative outcomes (clinical seizure cessation, all-cause mortality, admission to critical care). The data was collected on an intention-to-treat principle. Disagreements between the two authors were resolved by a third reviewer (FF).

2.6 Risk of Bias, Publication Bias, and Quality of Evidence

Two authors (FF and LL) independently assessed the risk of bias with the Cochrane Collaboration risk of bias tool across five domains (sequence generation, allocation concealment, blinding, detection bias, and attrition bias).[21] Each domain was assessed as either low, unclear, or high risk of bias. Disagreements between the two authors were resolved by a third reviewer (FF). Two authors (YZ and YF) independently rated the confidence in the estimates of effect for each outcome using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE).[22] We assessed the small-study effect using a visual estimate of the funnel plot and Egger's test, Begg's test, and Harbord's test when 10 or more

trials were pooled.[23]

2.7 Data synthesis

All statistical analyses were performed using RevMan (5.3.3; The Cochrane Collaboration). Pooled effect sizes were calculated using a random-effects model. For dichotomous outcomes, we calculated risk ratios (RR) and 95% CIs with the Mantel–Haenszel method. Statistical significance testing was 2-sided and $P<.05$ was considered statistically significant. Heterogeneity was assessed using the Chi^2 test and the I^2 test, with $I^2 > 50\%$ considered substantial.[24]

2.8 Trial sequential analysis

We conducted trial sequential analysis[25] for the primary outcome to explore whether cumulative data were adequately powered to evaluate outcomes. Trial sequential analysis was used to maintain an overall 5% risk of type I error, an anticipated relative risk reduction of 20.0%, and a control event rate of 67.0%. TSA viewer version 0.9.5.10 Beta (Copenhagen Trial Unit, Centre for Clinical Intervention Research, Copenhagen, DE. 2016) was used for analysis.

2.9 Subgroup analysis

Because of the concern that the effect of levetiracetam may differ in children and adults, we

stratified trials by age into two categories: children (age<18 years old) vs adults (age>18 years old).

2.10 Sensitivity analyses

Sensitivity analyses were done to explore potential heterogeneity by (1) excluding trials at each time, (2) using fixed-effect models, (3) excluding trials with a high risk of bias, (4) excluding trials with less than 100 patients.

3 Results

3.1 Study selection and study characteristics

Details of the study selection process are presented in Figure 1. We identified 965 studies in the systematic electronic literature search, and we also identified two additional trials after checking previous reviews. After removal of records according to pre-specified criteria, 13 full-text reports were reviewed for potential eligibility. After exclusion of incomplete reports[14, 26-31], six trials[15-18, 32, 33] were deemed eligible and included in the meta-analysis. The reasons for excluding trials that underwent full-text review are presented in Supplemental eTable 3.

The key characteristics of all included studies are summarized in Table 1 and eTable 4-5. Across the six trials, 765 participants were enrolled (390 randomized to levetiracetam, 375 randomized to phenytoin). The number of participants ranged from 44 to 286. The trials were published

between 2015 and 2019. Two trials[17, 18] were multicenter, and four[15, 16, 32, 33] were single-center.

3.2 Risk of Bias and Quality of Evidence

Risk-of-bias assessments are reported in Supplement eFigure 1 and 2. Three trials[15, 17, 18] were deemed at high risk of bias because of the unblinded design; one trial[32] was high risk for selection bias. Two trials[16, 33] were ranked as unclear risk. Key findings of GRADE assessment for main outcomes are shown in Supplement eTable 6.

3.3 Primary outcome

Of the six trials included in the meta-analysis, five trials were included in primary outcome assessement as they provided information on clinical seizure cessation within 15 min. The rates of seizure cessation within 15 min were 65.1 % (241/370) in the levetiracetam group and 64.3 % (222/345) in the phenytoin group. Compared with phenytoin, levetiracetam was not associated with a high rate of clinical seizure cessation (RR, 1.03; 95%CI, 0.92-1.16; I^2=23%; moderate-quality evidence; Figure 2). We did not perform analysis to detect small-study effects due to the low number of trials. The planned subgroup analysis of adult and pediatric patients was not performed, because there were no trials that only included adults (age > 18 years). Sensitivity analyses showed similar results in clinical seizure cessation for all of the following: excluding trials one at a time, using fixed-effect models, excluding trials with a high risk of bias, excluding trials with less than 100 patients (Supplement eTable 7). In trial sequential analyses of clinical

seizure cessation, the effect estimate lay outside the futility boundary for relative risks of 20%, meaning there is reliable evidence that overall, levetiracetam compared with phenytoin does not increase the rate of clinical seizure cessation by 20% (Supplement eFigure 3). However, in the pediatric subgroup, trial sequential analyses showed that the optimum size was not met (Supplement eFigure 4).

3.4 Secondary outcomes

The forest plots of secondary outcomes are shown in Figure 3. Similar with primary outcome, levetiracetam was not superior to phenytoin in good functional outcome (RR, 1.05; 95% CI, 0.90-1.23; I^2=0%), admission to critical care (RR, 1.15; 95% CI, 0.97-1.36; I^2=0%), or all-cause mortality (RR, 0.88; 95% CI, 0.40-1.97; I^2=0%).

4 Discussion

In this meta-analysis of 6 trials with a total of 765 patients, we did not detect a significant difference between phenytoin and levetiracetam for the treatment of established status epilepticus with regards to any outcome, including clinical seizure cessation within 15 minutes and safety. Both drugs were effective in controlling seizure activity after the failure of first-line treatment(benzodiazepines). These findings were not changed after sensitivity analyses were performed.

4.1 Comparison with other studies

A previous review with a similar analysis approach showed the absence of a statistically significant difference because of the lack of statistical power to detect a difference.[14] The previous review only included two small trials with a total of 157 adults. Hence there was considerable uncertainty around the conclusions and children could not be examined. Our findings are consistent with the previous review. However, our study differed in the following four aspects. First, our comparative analysis was the largest to date, comprising data, five times larger than the previous study, which has made it possible to improve the precision of the outcomes. Second, trial sequential analysis showed that our data meet the minimum information size, which increased the reliability of the results. Third, we have also provided absolute as well as relative risks and a formal rating of the quality of the evidence and documented the credibility of the primary outcome. Fourth, we quantified several new findings, including no difference between both groups in all-cause mortality, serious adverse events, non-serious adverse events, and admission to critical care.

After this study was submitted for initial review, an additional trial, the Established Status Epilepticus Treatment Trial (ESETT), was published.[13] The ESETT trial compared the efficacy and safety of levetiracetam, fosphenytoin, and valproate in children and adults with established status epilepticus, and found the three drugs were associated with similar incidences of seizure cessation. Though our results were similar to that of the ESETT trial, our study quality was inferior to the ESETT trial, which is a high-quality, double-blind, multi-site randomized trial that was well-powered to detect a difference between levitiracetam, fosphenytoin and valproate.

4.2 Strengths and limitations

We conducted this study based on an a priori protocol that defined a rigorous methodological approach based on the Cochrane Handbook. We also assessed the quality of evidence using GRADE (and found the quality for many critical outcomes moderate) and the minimum information size using in the trial sequential analysis in the overall analysis (and found our data meet the minimum information size).

This study had limitations. First, the main limitation of this study was the overall moderate methodological quality of included trials. The two large trials were delivered without blinding.

Second, the number of included trials was limited, and thus we were unable to evaluate the bias resulting from small-study effects (i.e. smaller studies show greater treatment effects than larger ones). However, the potential bias may be low because all included trials had negative results.

Third, although there were no significant difference between rates of adverse events in levetiracetam and phenytoin, levetiracetam showed a trend in reduced risk of serious adverse events. Also, caution is required when interpreting adverse events due to the extremely wide confidence intervals.

Fourth, trials included in this systematic review differed in their definition of convulsive status epilepticus, including the time of prolonged seizures and types of status epilepticus (generalized convulsive SE / focal motor SE). It may be a possible source of clinical heterogeneity.

Fifth, we used trial sequential analyses to control the risks of type I and type II errors. However, the use of trial sequential analyses has been criticized, and it appears more controversial to ignore the risks of random errors.[34] Interpretation of trial sequential analyses is complex and should be considered with caution.

Finally, while our meta-analysis specified the second-line treatment, it did not specify

demonstrated refractoriness to the first-line benzodiazepine treatment. Four of six trials described in their methods section how patients who failed the first-line benzodiazepine was enrolled and patients who responded to benzodiazepine was excluded. However, two trials allocated second-line treatments immediately after benzodiazepine administration.[15,33] The two trials did not provide time for observing the cessation of epileptic activity, and some of the patients may have seizure cessation not attributable to the second-line treatment, leading to clinical heterogeneity in our meta-analysis.

4.3 Implications

In the past decade, guidelines recommend phenytoin as the treatment of established status epilepticus after the failure of first-line treatment with benzodiazepines.[6-8] The use of alternative drugs had been limited by the lack of high-quality evidence for this indication. Results of our meta-analysis of randomized trials suggests that levetiracetam and phenytoin had similar efficacy and safety for the treatment of established status epilepticus. Another recently published head-to-head trial provided stronger evidence for the same conclusion. In light of the evidence, recommendations for second-line treatment could be expanded.

Nonetheless, our findings should be interpreted with caution because a planned subgroup analysis stratified by age was not performed. The subgroup analysis was not conducted was due to a lack of trials that enrolled only adults, and the sample size of trials conducted in children failed to meet the optimum size in trial sequential analysis.

5 Conclusions

This meta-analysis did not find evidence supporting that levetiracetam was superior to phenytoin in cessation rate of clinical seizure within 15 minutes.

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines

Author contributions:

FF conceived the study and designed the protocol.

YZ and AF performed the literature search.

YZ and LJ selected the studies.

YZ and YF extracted the relevant information.

LM and DJ synthesized the data.

LL wrote the first draft of the paper.

YZ, AF, LJ, YF, LM, DJ, WC and FF critically revised successive drafts of the paper.

FF is the guarantor of the review.

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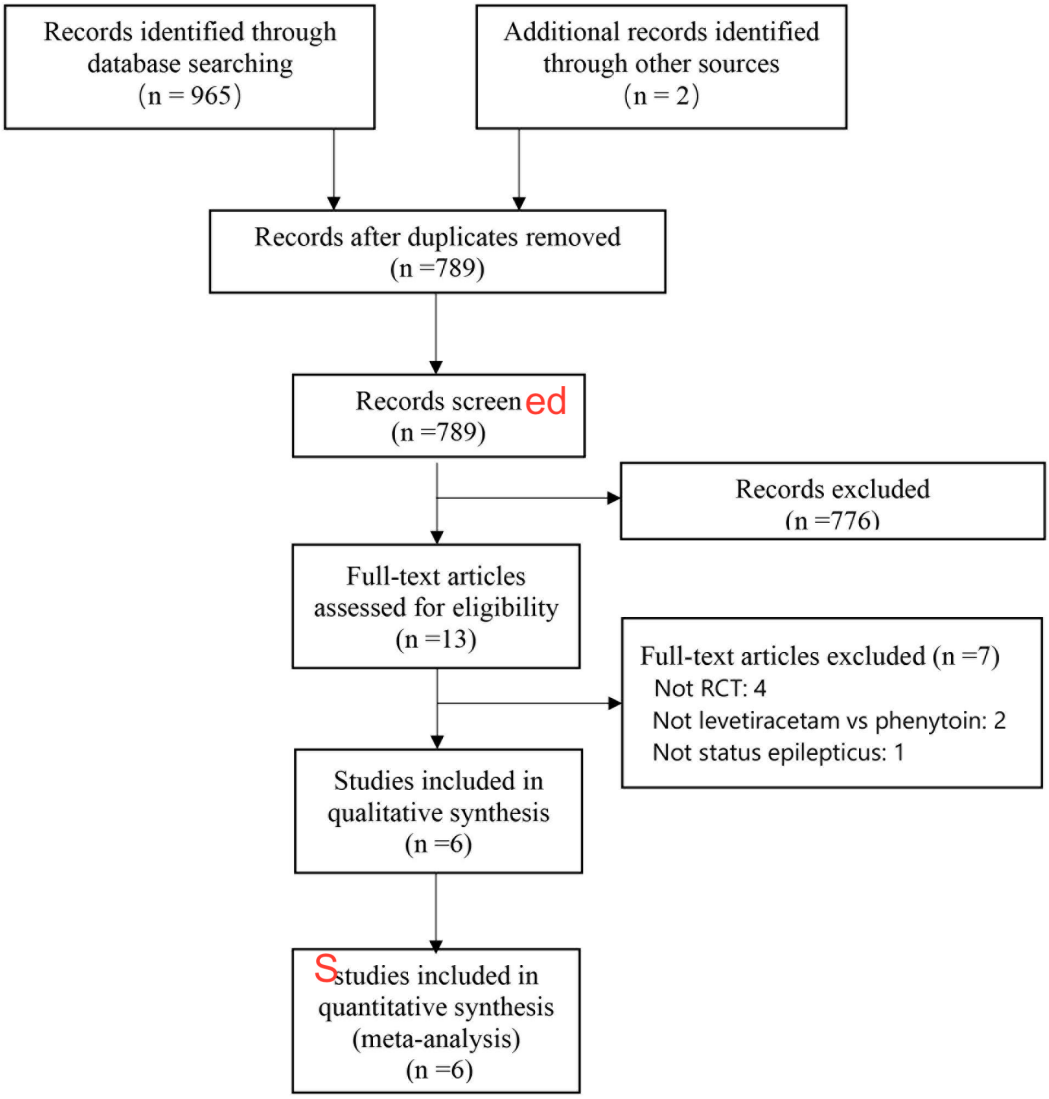
Figure descriptions:

Figure 1 Search strategy and final included and excluded studies

Figure 2 Association of levetiracetam versus phenytoin with clinical seizure cessation.

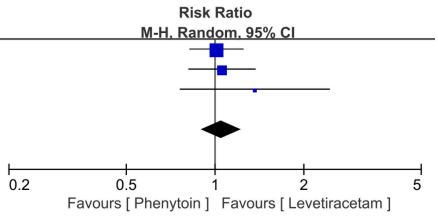
Figure 3 Association of levetiracetam versus phenytoin with all-cause mortality, admission to critical care, and good functional outcome


Records identified through database searching (n = 965)
Additional records identified through other sources (n = 2)
Records after duplicates removed (n =789)
Records screened (n =789)
Records excluded (n =776)
Full-text articles assessed for eligibility (n =13)
Full-text articles excluded (n =7)
Not RCT: 4
Not levetiracetam vs phenytoin: 2
Not status epilepticus: 1
Studies included in qualitative synthesis (n =6)
Studies included in quantitative synthesis (meta-analysis) (n =6)

A. Good functional outcome

Study or Subgroup	Levetiracetam Events	Total	Phenytoin Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Mundlamuri 2015	31	37	29	35	56.4%	1.01 [0.82, 1.24]	2015
Chakravarthi 2015	19	22	18	22	36.4%	1.06 [0.82, 1.37]	2015
Gujjar 2017	12	22	12	30	7.2%	1.36 [0.76, 2.44]	2017
Total (95% CI)		**81**		**87**	**100.0%**	**1.05 [0.90, 1.23]**	
Total events	62		59				

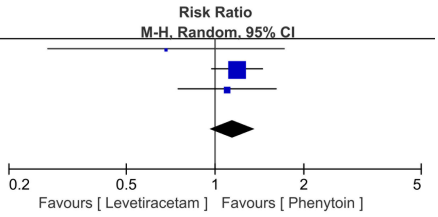
Heterogeneity: Tau² = 0.00; Chi² = 1.10, df = 2 (P = 0.58); I² = 0%
Test for overall effect: Z = 0.61 (P = 0.54)



B. Admission to critical care

Study or Subgroup	Levetiracetam Events	Total	Phenytoin Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Gujjar 2017	5	22	10	30	3.5%	0.68 [0.27, 1.71]	2017
Lyttle 2019	97	152	72	134	76.1%	1.19 [0.97, 1.45]	2019
Dalziel 2019	39	119	34	114	20.4%	1.10 [0.75, 1.61]	2019
Total (95% CI)		**293**		**278**	**100.0%**	**1.15 [0.97, 1.36]**	
Total events	141		116				

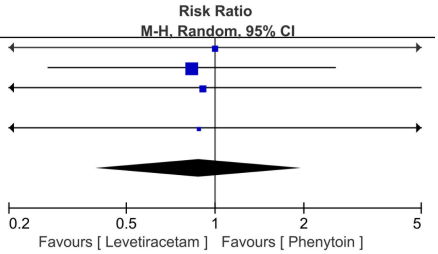
Heterogeneity: Tau² = 0.00; Chi² = 1.43, df = 2 (P = 0.49); I² = 0%
Test for overall effect: Z = 1.56 (P = 0.12)



C. All-cause mortality

Study or Subgroup	Levetiracetam Events	Total	Phenytoin Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Chakravarthi 2015	2	22	2	22	18.4%	1.00 [0.15, 6.48]	2015
Mundlamuri 2015	5	50	6	50	51.1%	0.83 [0.27, 2.55]	2015
Gujjar 2017	2	22	3	30	22.1%	0.91 [0.17, 4.99]	2017
Dalziel 2019	0	70	0	72		Not estimable	2019
Lyttle 2019	1	152	1	134	8.4%	0.88 [0.06, 13.96]	2019
Total (95% CI)		**316**		**308**	**100.0%**	**0.88 [0.40, 1.97]**	
Total events	10		12				

Heterogeneity: Tau² = 0.00; Chi² = 0.03, df = 3 (P = 1.00); I² = 0%
Test for overall effect: Z = 0.31 (P = 0.76)



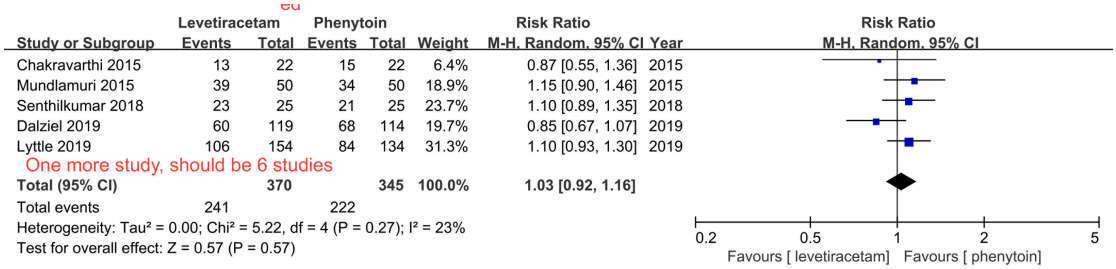

Levetiracetam
Phenytoin
Risk Ratio
Risk Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI Year
M-H, Random, 95% CI
Chakravarthi 2015 13 22 15 22 6.4% 0.87 [0.55, 1.36] 2015
Mundlamuri 2015 39 50 34 50 18.9% 1.15 [0.90, 1.46] 2015
Senthilkumar 2018 23 25 21 25 23.7% 1.10 [0.89, 1.35] 2018
Dalziel 2019 60 119 68 114 19.7% 0.85 [0.67, 1.07] 2019
Lyttle 2019 106 154 84 134 31.3% 1.10 [0.93, 1.30] 2019
One more study, should be 6 studies
Total (95% CI) 370 345 100.0% 1.03 [0.92, 1.16]
Total events 241 222
Heterogeneity: Tau² = 0.00; Chi² = 5.22, df = 4 (P = 0.27); I² = 23%
Test for overall effect: Z = 0.57 (P = 0.57)
0.2
0.5
1
2
5
Favours [levetiracetam]
Favours [phenytoin]

Table 1 Characteristics of trials included

Trials	Country	Site	Age range	Patients, N		Mean age		Female, %		Initial Dosages	
				LEV	PHT	LEV	PHT	LEV	PHT	LEV	PHT
Mundlamuri 2015	India	1	> 15	50	50	34.78±13.64	33.24±13.39	36	44	25 mg/kg	20 mg/kg at 50 mg/min
Chakravarthi 2015	India	1	> 14	22	22	39.00±18.40	31.82±12.68	45	32	20 mg/kg at 100 mg/min	20 mg/kg at 50 mg/min
Gujjar 2017	Oman	1	> 15	22	30	38±19	37±19	41	30	30 mg/kg over 30 min	20 mg/kg over 30 min
Senthilkumar 2018	India	1	0.25-12	25	25	2.28±2.19	3.34±3.36	28	36	30mg/kg over 7 min	20mg/kg
Dalziel 2019	Australia, New Zealand	13	0.25-16	119	114	3.8±3.8	4.0±3.9	50	54	20mg/kg over 5 min	20 mg/kg over 20 min
Lyttle 2019	UK	30	0.5-18	152	134	2.7	2.7	51	46	40 mg/kg over 5 min	20 mg/kg (max 2g)

PHT: phenytoin; LEV: levetiracetam