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# A META-ANALYSIS OF THE EFFICACY AND SAFETY OF ADJUNCTIVE PERAMPANEL FOR THE TREATMENT OF REFRACTORY FOCAL-ONSET SEIZURES IN EPILEPTIC PATIENTS

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## ABSTRACT

### Objective

The usage of anti-seizure medications (ASMs) has increased over the previous decade, yet the burden of treating drug-resistant epilepsy has not decreased. This meta-analysis was carried out to determine the best dose of Perampanel (PER) as a new adjunctive treatment for drug-resistant seizures.

### Method

We examined through ScienceDirect, PubMed, and the Central Register of Controlled Trials (CENTRAL) for research that had been published between their

start and February 1, 2021. characteristics of the research, patients, and treatment regimen, concurrent ASMs, and clinical results were taken out. The practical result was a 50%, 75%, or 100% decrease in the frequency of convulsive seizures, and the safety result was the percentage of drug withdrawal and negative side effects. The inverse variance approach was used to estimate odds ratios (OR) for 95% confidence intervals (CI).

**Result**

Four trials totalled 2187 people (1569 in the PER group and 618 in the placebo group). Results revealed that 8 or 12 mg per day had the greatest impact on all three outcomes, with no statistically significant difference between 8 and 12 mg per day (seizure-free, 3.5% vs. 3.7%, P =.85); 50% reduction, 35.5% vs. 36.1%; 75% reduction, 17.8% vs. 19.1%). Additionally, a larger percentage of treatment-emergent adverse events (TEAE) that led to dosage reduction or discontinuation occurred with 12-mg PER compared to 8-mg (8.7% vs. 17.0%; P .00001). Dizziness, somnolence, weariness, and irritability were the reported adverse events (AEs) (significantly linked with adjunctive PER).

**Significance**

In patients with refractory epilepsy, adjunctive treatment with PER was related to a greater reduction in seizure frequency than placebo and a higher frequency of adverse events (AEs). For the majorityof research participants, PER at a dose of 8 mg per day appeared to have the best efficacy-to-tolerance ratio.

**Keywords** Epilepsy, Anti-seizure medication, Perampanel.



## INTRODUCTION

Around 80 out of every 100,000 persons are thought to have epilepsy, and 5 out of every 1000 are thought to have it. There are roughly 70 million epilepsy sufferers worldwide.1,2 Symptoms determine how epilepsy is treated. Even though many epilepsy patients can control theirseizures, more than one-third of seizures are stilluncontrollable3. Epileptic seizures that go unchecked are probably a risk factor for reduced life expectancy, disability, and early death along with significant physical and mental impairment.4 The burden of treating drug-resistant epilepsy has not decreased despite the rise in the availability and use of anti-seizure drugs (ASMs) over the past few years. There is still a need for novel, efficient therapeutic approaches.5 The efficacy and safety of more recent medications also need to be reviewed on a regular basis.

An antagonist of the alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptor that is orally active is called Perampanel (PER). This receptor is essential for the genesis, propagation, and fast excitatory synaptic transmission of epileptic activity.6 PER (for patients 18 years of age or older) received approval from the European Union and the US in 2014, and more than 40 nations have since followed suit.7,8 The risk of treatment-emergent adverse events (TEAEs) was shown to be present in all anti-seizure drugs (ASMs). As a result, reducing TEAEs is crucial while taking ASMs. The effectiveness and safety of adjunctive PER for the treatment of refractory focal-onset seizures in epilepsy patients are evaluated in this meta-analysis.

## METHODS

### Search Methodology

"Perampanel"[Mesh] or "3-(2-cyanophenyl)-5-(2-pyridyl)-1-phenyl-1,2-dihydr opyridin-2-one" AND "refractory partial-onset seizures" [Mesh] AND "randomised controlled trial" [ptyp] are examples of similar compounds. Other criteria were not applied. The following entry criteria were used to choose studies: phase III, randomised, double-blind, placebo-controlled, parallel-group design with 6-week baseline observation and a 19-week double-blind treatment phase (6-week titration period and 13-week maintenance period). The following qualifications must be met by participants to be included: age >12, focal-onset (partial-onset) seizures diagnosed, at least two ASM failures in the previous two years, at least five focal seizures in the baseline phase lasting at least six weeks, and stable doses of 1-4 approved concomitant ASMs being taken. The following studies were excluded from consideration: non-English studies, RCT publications using the same experimental

data, articles not documenting a 50% decrease in seizure frequency, and articles utilising arbitrary drug dosages. There is currently no PROSPERO registration number. The specific process is shown in Figure 1:

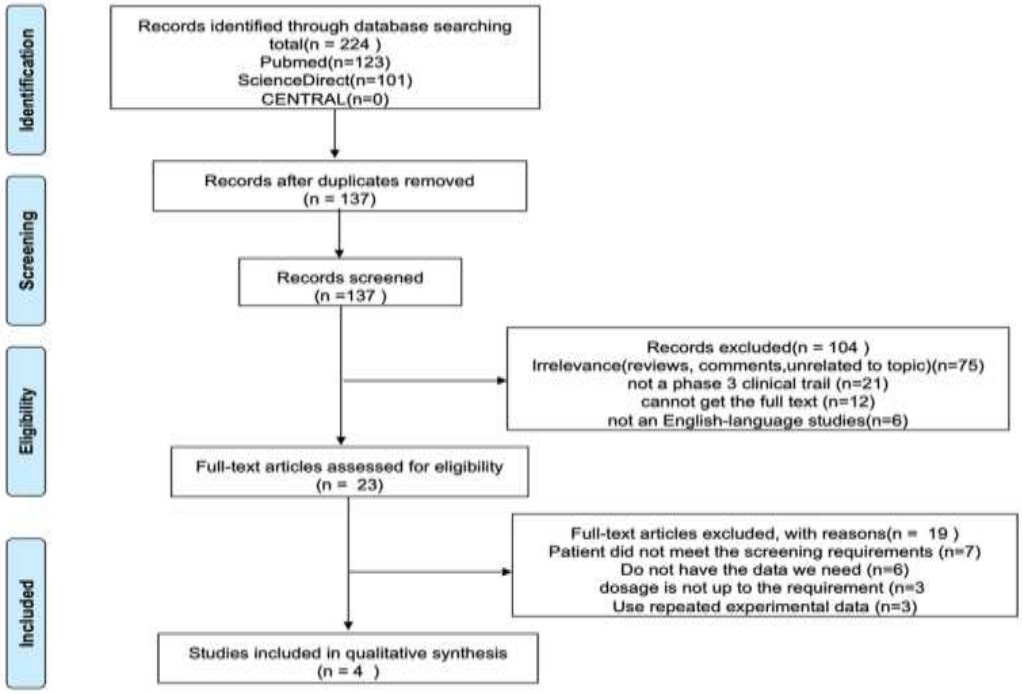


**FIGURE 1: Flow diagram of study selection process**

## OUTCOME MEASURES

The key result was the responder rate, which was measured as the proportion of patients in the European Union who saw a 50% decrease in seizure frequency compared to baseline during the maintenance phase. Responder rate is not a continuous variable, but rather a single point within the full response. Therefore, the 50% responder rate offers less data from all potential responses; it can also be less sensitive. When the responder rate was increased to 75%, there were more noticeable improvements than with the placebo. Therefore, the secondary endpoint was set as a 75% decrease in seizure frequency and seizure free.

These safety results were obtained: 1. the percentage of patients who discontinue therapy for whatever reason; 2. all TEAEs connected to PER, such as irritation, weariness, headache, nausea, upper respiratory tract infection, and gait disruption.

## INFORMATION AND A DETERMINATION OF THE BIAS RISK

We adhere to the requirements of the study and enter the following data into a structured Excel data table in order to guarantee the consistency of the data collection for each study: Patient characteristics (such as age, gender, aetiology, duration of disease, sample size, titration time, and maintenance time), research characteristics (such as sample size. The quality of selection, performance, detection, attrition, and reporting biases for each qualified trial was evaluated using assessment forms from the Cochrane Manual (including complications and treatment regimen), concurrent ASMs, and clinical outcomes. 2011. 9

## STATISTICAL ANALYSIS

We generated pooled effect estimates, such as odd ratios (OR) and associated 95% confidence intervals (CI), for the meta-analysis using Cochrane Collaboration's Review Manager software (RevMan 5.4). A nominal significance level of.05. was used to determine statistical significance. The decision between a fixed-effect model and a random-effect model was made based on the heterogeneity index $I^2$.

## RESULTS

### Study characteristics

The database and trial register searches resulted in the initial discovery of 284 records. For a thorough analysis, four randomised controlled trials (RCTs) were gathered.10–13. The essential characteristics of the studies are mentioned in Table 1.

| Article | Inclusion criteria | Race | Female gender, n (%) | Mean age (years) | Intervention group | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | Placebo | PER 2 mg | PER 4 mg | PER 8 mg | PER 12 mg |
| Jacqueline A. French 2013[12] | Diagnosis of simple or complex focal seizures permitted only one inducer ASM and must have been on a stable dose of any concomitant benzodiazepines | White (322) Asian (42) Others (22) | 65 (47.8)/64 (49.6)/71 (58.7) | 34.4 (13.6)/36.7 (14.4)/ 35.5 (14.1) | n = 136 | | | n = 129 | n = 121 |
| Jacqueline A. French 2012[14] | Diagnosed with focal-onset seizures, with stable doses of 2-3 approved ASMs | White (334) Asian (4) Others (50) | 67 (55.4)/68 (51.1)/65 (48.5) | 35.6 (14.7)/35.8 (14.2)/36.7 (14.6) | n = 121 | | | n = 133 | n = 134 |
| T. Nishida 2017[13] | | / | 90 (48.6)/95 (52.8)/84 (48.8)/92 (54.4) | 33.4 (12.6)/33.8 (13.6)/33.6 (12.2)/34.6 (12.8) | n = 185 | n = 180 | n = 172 | n = 169 | |
| GL Krauss 2012[15] | Diagnosed with simple or complex focal-onset seizures, with stable doses of 2-3 approved ASMs | White (459) Asian (244) Others (3) | 89 (50.9)/94 (54.0)/84 (48.0)/93 (51.7) | 34.5 (13.2)/33.1 (13.2)/33.6 (14.1)/32.3 (12.3) | n = 175 | | n = 174 | n = 175 | n = 180 |

## Risk of Bias Assessment

Four studies had a low risk of bias since they were multicenter, randomized, double-blinded, placebo-controlled, parallel-group trials (Table 2).

| Outcome of subgroup | Number of studies | Participants | $I^{2,}$ % | Odds ratio (95% CI) | P |
|---|---|---|---|---|---|
| 1.1 50% reduction in the seizure frequency | 4 | 2186 | 36% | 1.96 [1.56, 2.45] | <.00001 |
| 1.1.1 per 2 mg/d vs placebo | 1 | 360 | 0% | 1.18 [0.70, 2.00] | .53 |
| 1.1.2 per 4 mg/d vs placebo | 2 | 745 | 0% | 1.45 [1.02, 2.08] | .04 |
| 1.1.3 per 8 mg/d vs placebo | 4 | 1229 | 0% | 2.12 [1.63, 2.75] | <.00001 |
| 1.1.4 per 12 mg/d vs placebo | 3 | 859 | 40 | 2.53 [1.87, 3.44] | <.00001 |
| 1.2 75% reduction in the seizure frequency | 4 | 2168 | 0% | 2.74 [1.93, 3.89] | <.00001 |
| 1.2.1 PER 2 mg/d vs placebo | 1 | 256 | 0% | 1.94 [0.87, 4.34] | .1 |
| 1.2.2 PER 4 mg/d vs placebo | 2 | 700 | 0% | 1.73 [1.04, 2.88] | P=.03 |
| 1.2.3 PER 8 mg/d vs placebo | 4 | 1283 | 0% | 3.01 [2.04, 4.43] | p<.00001 |
| 1.2.4 PER 12 mg/d vs placebo | 3 | 865 | 0% | 3.29 [2.10, 5.15] | p<.00001 |
| 1.3 Seizure freedom during the treatment | 4 | 2173 | 0% | 3.24 [1.42, 7.83] | .005 |
| 1.3.1 PER 2 mg/d vs placebo | 1 | 260 | 0% | 1.55 [0.26, 9.39] | P=.63 |
| 1.2.2 PER 4 mg/d vs placebo | 2 | 700 | 0% | 3.20 [1.02, 10.00] | P=.05 |
| 1.2.3 PER 8 mg/d vs placebo | 4 | 1220 | 0% | 3.51 [1.45, 8.51] | P=.005 |
| 1.2.4 PER 12 mg/d vs placebo | 3 | 861 | 0% | 3.88 [1.35, 11.14] | P=0.1 |

We compared four PER dosage options (2, 4, 8, or 12 mg) with placebo; pooled data from the four RCTs revealed that all of the PER 4, 8, and 12-mg groups had a superior response compared with the placebo group, and the PER doses of 8 and 12 mg appeared to be more effective than the 4-mg dose of PER (8 mg: 50% reduction, 25.6% vs 35.5%, P =.002; 75% reduction, 12.4% vs 19.1%, P=.01; seizure-free,3.5% vs.01; seizure-free,3.5% vs.7%, P=.86

When we evaluated the 8 mg and 12 mg PER dosages for three effectiveness objectives (50% reduction, 35.5% vs 36.1%, P =.84; 75% reduction, 17.8% vs 19.1%, P =.64; seizure-free, 3.5% vs 3.7%, P =.85), the data revealed that there is no discernible difference between the doses of 8 and 12 mg. Figure 2 shows the specifics of the seizure decrease by 50%. In conclusion, the effectiveness of various PER doses is as follows:

The minimal effective dose of PER may be 4 mg/d since there was no statistically significant difference between the 2 mg/d dose and the placebo. 8 = 12 mg > 4 mg.

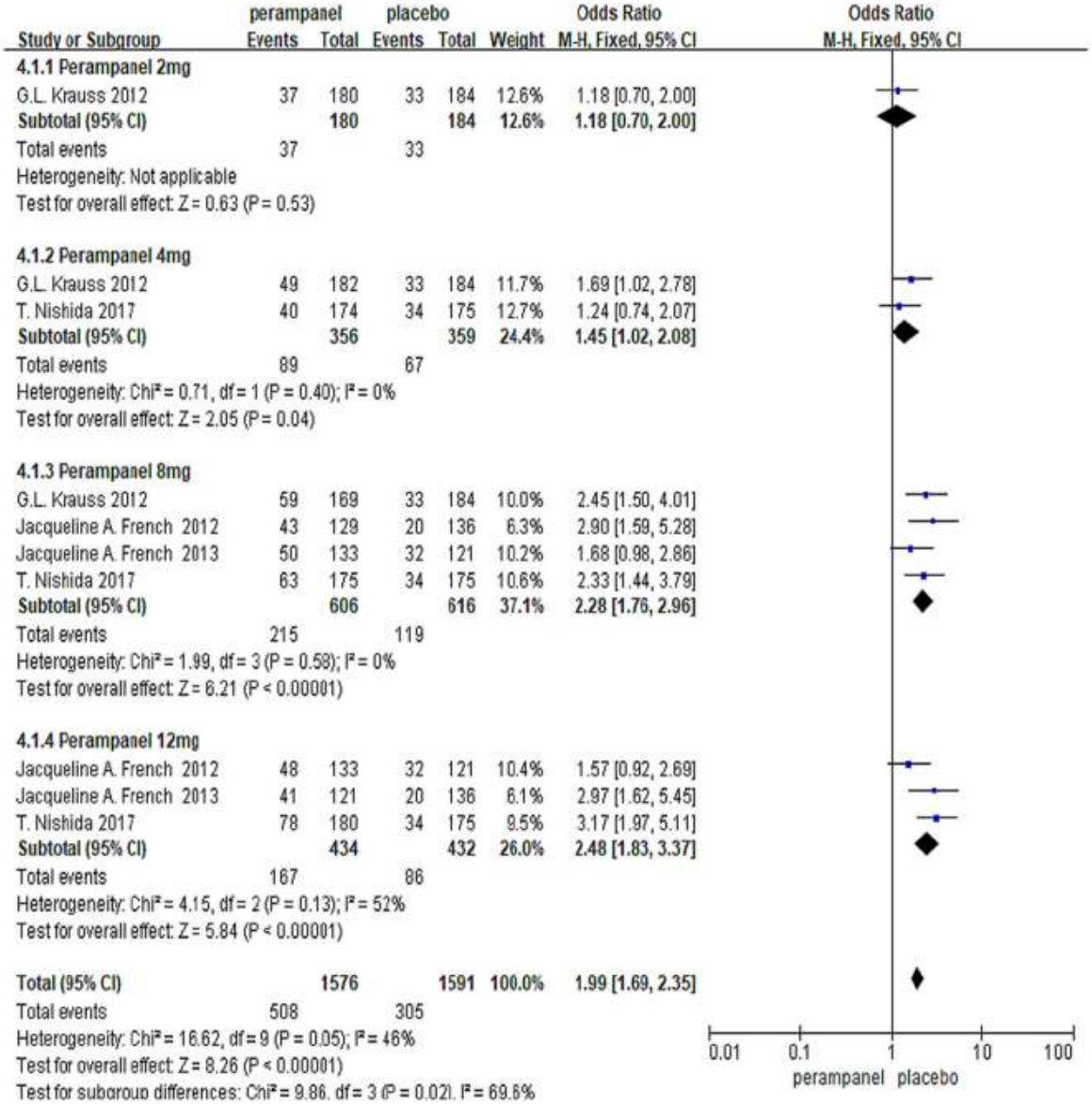


**FIGURE 2: Effect of Perampanel on 50% reduction in refactory focal-onset seizure**

## Treatment withdrawal and adverse events

In withdrawal from the treatment, and negative effects Patients withdrew from 152 (9.52%) and 27 (4.3%) trials overall. from the research in the PER added and placebo groups, respectively, due to medication-related TEAEs (OR 2.50, 95% CI 1.64-3.82; I 2 = 0%; P < .0001). Patients' incidents are removal from the research because of TEAEs caused by drugs were greater when supplementing with 2, 8, and PER. Comparing 12 mg to the placebo group (2 mg, 6.7% against 3.8%, P < .02; 8 mg, 8.4% versus 4.4%, P < .004; 12 mg, 17.0% vs 4.6%, P .00001). 4 mg of PER supplementation showed no discernible change (3.7% as opposed to 3.6%, P < .92) (Table 3).

Additionally, a larger percentage of trial withdrawals occurred with 12-mg PER compared to 8-mg PER (8.7% vs. 17.0%;P < .00001) significant adverse events that need dose adjustment or termination (18.5% vs 32.0%; P .00001) absent a notable increase in performance. In conclusion, the safety of various PER dosages is arranged as follows: 4 > 8 > 12 mg. 0.02 grams, 2 mg had not been utilized in this comparison because no effectiveness, hence we viewed the 2 mg dose as safemeaningless.

The PER-added group experienced more treatment-related TEAEs than the control group (59.6% vs 37.9%; P .00001) (Table 3), which also has to do with dosage. the TEAEs supplementation with 4, 8, and 12 mg of PER is more potent. Compared to those who received a placebo (4 mg, 45.4% vs. 30.7%, P = .0001; 8 mg, 61.2% versus 34.8%, P < .00001; 12 mg, 75.2% vs 37.0%, P = .0002). When 2 mg of PER were supplemented, there was no discernible change (37.2% vs. 31.9%, P =.29) (Table 3).

The prevalence of severe TEAEs did not change statistically (5.1% vs. 5.1%; P =.88). There was a significant difference between the PER-added group and the placebo group (29.1% vs. 8.1%; P .00001) and dizziness was the most frequent TEAE. The incidence of major TEAEs was also as follows: somnolence (16.0% vs 7.2%; P .001), headache (8.6% vs 10.0%; P =.94), fatigue (7.2% vs 4.4%; P =.03), upper respiratory tract infection (5.0% vs 3.6%; P =.28), nasopharyngitis (8.4% vs 8.0%; P =.86), gait disturbance (3.8% vs 2.2%; 0.06), ), nausea (3.3% vs 2.8%; 0.72), and falls (11.2% vs 6.6%; P = .12) irritability (7.1% vs 2.3%; 0.003), rash (2.4% vs 1.1%; P = .31 (Table 4).

TABLE 3: Treatment dropout between perampanel (PER) and placebo

| Outcome or Subgroup | Studies | PER | Placebo | $I^2$ (%) | Odd Ratio (95%Cl) | P |
|---|---|---|---|---|---|---|
| Treatment dropout | | | | | | |
| Per any dose | 4 | 152/1569 (9.5%) | 27/618(4.4%) | 0 | 2.50[1.64,3.80] | <.001 |
| Per 2mg/d | 1 | 12/180 (6.7%) | 7/185(3.8%) | 0 | 1.82[0.70-4.72] | .02 |
| Per 4 mg/d | 2 | 13/384 (3.7%) | 13/361(3.6%) | 0 | 1.04 [0.47,2.27] | .92 |
| Per 8 mg/d | 4 | 53/633 (8.4%) | 27/617(4.4%) | 5 | 2.00 [1.24,3.22] | .004 |
| Per 12 mg/d | 3 | 74/435 (17.0%) | 20/433(4.6%) | 01 | 4.53 [2.53-7.08] | <.001 |
| Any TEAE leading to dose reduction/ interruption | | | | | | |
| Per any dose | 4 | 286/1569 (18.2%) | 24/618(3.9%) | 0 | | |
| Per 2mg/d | 1 | 3/180 (1.7%) | 6/185(3.2%) | 0 | 0.51 [0.12,2.05] | .34 |
| Per 4 mg/d | 2 | 32/348 (9.2%) | 13/361(3.6%) | 0 | 2.13[1.20,3.79] | .01 |
| Per 8 mg/d | 4 | 112/606 (18.5%) | 24/618(3.9%) | 0 | 5.41 [3.57, 8.21] | <.001 |
| Per 12 mg/d | 3 | 139/435 (32.0%) | 18/433(4.2%) | 0 | 9.87 [6.24, 15.62] | <.001 |
| Any TEAE | | | | | | |
| Per any dose | 4 | 1026/1569 (75.6%) | 411/618(66.5%) | 0 | 0.98 [0.92,1.05] | .62 |
| Per 2mg/d | 1 | 111/180 (61.7%) | 101/185(54.6%) | 0 | 1.13 [0.95,1.35] | .17 |
| Per 4 mg/d | 2 | 232/348 (66.7%) | 218/361(60.4%) | 27% | 1.10[0.99,1.23] | .09 |

| | | | | | | |
|---|---|---|---|---|---|---|
| Per 8 mg/d | 4 | 479/570 (84.0%) | 411/682(60.3%) | 91% | 1.25 [1.02, 1.55] | .03 |
| Per 12 mg/d | 3 | 383/435 (88.0%) | 310/433(71.6%) | 61% | 1.21 [1.09, 1.35] | .0004 |

**Any treatment related TEAE**

| | | | | | | |
|---|---|---|---|---|---|---|
| Per any dose | 4 | 936/1569 (59.7%) | 234/618(37.9%) | 62 | 2.72 [2.23,3.31] | .00001 |
| Per 2mg/d | 1 | 67/180 (37.2%) | 59/185(31.9%) | 0 | 1.17[0.88,1.55] | .29 |
| Per 4 mg/d | 2 | 158/348 (45.4%) | 111/361(30.7%) | 0 | 1.48[1.22,1.79] | .0001 |
| Per 8 mg/d | 4 | 292/477(61.2%) | 169/485(34.8%) | 0 | 1.70 [1.49, 1.95] | <.00001 |
| Per 12 mg/d | 3 | 236/314 (75.2%) | 110/297(37.0%) | 80% | 2.00 [1.40, 2.86] | .0002 |

**TABLE 4: TEAEs between perampanel (PER) and placebo**

| Outcome | Studies | PER | Placebo (%) | $I^2$ (%) | Odd Ratio (95% CI) | P |
|---|---|---|---|---|---|---|
| All TEAEs | 4 | 936/1569 (59.7%) | 234/618(37.9%) | 62 | 2.72 [2.23, 3.31] | <.001 |
| Dizziness | 4 | 458/1569 (29.2%) | 50/619(8.1%) | 80 | 4.83 [3.55,6.58] | <.001 |
| Somnolence | 4 | 215/1569 (45.4%) | 45/618(7.3%) | 64 | 2.45 [1.75, 3.41] | <.001 |
| Headache | 4 | 292/477(61.2%) | 62/618(10.0%) | 0 | 1.01 [0.74, 1.39] | .94 |
| Fatigue | 3 | 936/1569 (59.7%) | 22/497(4.4%) | 0 | 1.74 [1.07, 1.39] | .03 |
| Upper respiratory tract infection | 3 | 67/180 (37.2%) | 13/361(3.6%) | 0 | 1.41 [0.76, 2.83] | .28 |
| Nasopharyngitis | 2 | 158/348 (45.4%) | 29/361(8.0%) | 0 | 0.96 [0.62, 1.48] | .86 |
| Gait disturbance | 2 | 292/477(61.2%) | 11/482(2.3%) | 0 | 1.88 [0.97, 3.66] | .06. |
| Irritability | 2 | 236/314 (75.2%) | 7/297(2.4%) | 41 | 3.48 [1.54, 7.83] | .003 |
| Rash | 1 | 936/1569 (59.7%) | 2/176 (1.1%) | 0 | 2.18 [0.49,9.77] | .31 |
| Nausea | 1 | 67/180 (37.2%) | 5/176(2.8%) | 0 | 1.20 [0.44, 3.28] | .72 |
| Fall | 1 | 158/348 (45.4%) | 8/121(6.6%) | 0 | 1.79 [0.79, 4.02] | .16 |

## DISCUSSION

Despite receiving appropriate medical care, one-third of individuals' epilepsy is still uncontrolled. In China in 2019, PER has been marketed as a third-generation ASM and an adjunctive treatment for focal-onset seizures. PER was advised for treatment-resistant adult focal epilepsy (level A) in the 2018 American Academy of Neurology and American Epilepsy Society guidelines.14 Oral PER possesses superficial pharmacological properties, including quick absorption from the gastrointestinal tract and a terminal half-life of roughly 70–120 hours. Steadystate plasma concentrations can be attained within 14 days of oral dosing.15 Plasma concentrations

of ASM measured concurrently are unaffected by PER.16 According to the findings of our meta-analysis, PER supplemental therapy at daily doses of 4, 8, or 12 mg significantly decreased the number of seizures in patients with refractory focal seizures that were infrequently stopped because to intolerable TEAES. Because there is no statistically significant difference between the 2 mg/d dose and placebo, the lowest effective dose of PER may be 4 mg/d. However, since only one investigation used 2 mg, its efficacy needs to be confirmed in more studies.

The PER doses of 8 mg and 12 mg are more effective than 4 mg, and there is no significant difference in efficacy between the PER doses of 8 and 12 mg. Furthermore, a tiny percentage of individuals developed seizures, which could be a dose-dependent phenomena; although the small number, this trend was statistically significant.

8 mg and 12 mg PER doses are more effective than 4 mg, and there is no significant difference in efficacy between the PER doses of 8 and 12 mg. Furthermore, a small proportion of people had seizures, which could be a dose-dependent phenomenon; despite the small number, this trend was statistically significant.

Patients reported more TEAEs and a higher fraction of trial withdrawal after taking the 12-mg dose is less significant than that of the 8 mg, thus PER 8 mg/d may be the best alternative. There are, however, other reasons for a considerable number of individuals to accept the 12 mg.17 The 12-milligram dosage may be a necessary alternative in order to accomplish the goal of a more significant reduction in seizures and free seizures in those who can tolerate an 8-mg dose but do not reach optimal response.

Furthermore, even though the maintenance period is twice as long as the titration period, the frequency of TEAEs during the maintenance period is lower than during the titration period, showing that they are transient, with no increase in the incidence of TEAE with time and no potential tolerance.10,18 The low or non-existence of these TEAEs after 6 months to 1 year of treatment is further evidence that long-term treatment with PER is safe and well tolerated.18

In these four RCTs, three patients died: one from sudden cardiac death in the placebo group, one from an unknown cause in the PER 8-mg group, and one from convulsion during baseline. Because of the low frequency of incidents, it is uncertain whether drugs were the cause of the deaths. In addition, three patients in the placebo group, one in the PER 2-mg group, two in the PER 8-mg group, and two in the PER 12 mg group displayed suicidal intentions. Again, we don't know for sure whether the suicidal tendencies were caused by the medicines. There was no statistically significant difference in severe TEAEs between the PER and placebo groups, according to the data. Overall, the 12-mg group had a higher rate of psychotic severe TEAEs than the other dose or placebo groups. Although there was no statistically significant difference between the placebo and PER groups in terms of severe adverse events, the proportion of TEAEs leading to cessation and dosage reduction/interruption was higher in the PER group than in the placebo group. In most situations, dose decrease rather than PER discontinuation was employed to treat TEAEs.

## CONCLUSION

Perampanel is a treatment option for refractory focal epilepsy. Adjunctive PER therapy was related with a greater reduction in the frequency of seizures in individuals with refractory epilepsy than placebo, but with a higher frequency of adverse events. A daily dose of PER 8 mg is thought to be the optimal dosing strategy. To improve patient tolerance, we recommend gradually increasing and decreasing the dose while starting or stopping.

More study will be conducted in the future to explain the full therapeutic potential and clinical importance of this latest ASM.

## THIS STUDY'S STRENGTHS AND LIMITATIONS

- This study looked at the efficacy and safety of various dosages of adjunctive PER in patients with focal seizures.
- The efficacy and safety evaluations in this meta-analysis are mostly based on daily doses of PER estimations of seizure response during the maintenance phase, which is the most accurate phase to represent steady-state drug levels throughout the treatment duration.
- The efficacy and safety evaluations in this meta-analysis are mostly based on daily doses of PER estimations of seizure response during the maintenance phase, which is the most accurate phase to represent steady-state drug levels throughout the treatment duration.
- This meta-analysis inherited the four RCTs' inherent limitations, such as the short duration of maintenance and the potential impact of concurrent medication.

- There is no information in this meta-analysis about the efficacy, tolerability, and safety of PER monotherapy during pregnancy and lactation.

## CONFLICT OF INTEREST

There are no conflicts of interest to disclose for either of the authors. We confirm that we have read the Journal's position on ethical publication problems and that our report adheres to their criteria.

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