Effects of Perampanel on Seizure Control, Cognition, Behavior, and Psychological Status in Patients With Epilepsy: A Systematic Review

Background and Purpose Thoroughly acquainting physicians with the effects of antiseizure medications (ASMs) is essential for developing appropriate therapeutic regimens for seizure management. This review summarizes the available evidence regarding patients receiving the antiseizure agent perampanel (PER) and its effects on the cognition, behavior, and psychological status of patients.

Methods The PubMed and Google Scholar databases were searched for all relevant articles published during 2015–2021 and without any other publication limitations, and also manually searched the reference lists in the identified articles. Outcomes of interest were changes in seizure frequency relative to baseline, 50% responder rate, seizure-free rate, and retention rate (proportion of participants continuing PER at study endpoints). Safety outcomes included adverse effects and the percentage of patients experiencing effects on cognitive, psychiatric, and behavioral symptoms.

Results We identified 139 studies, of which 28 were included after screening. Most studies found reduced seizure frequencies and satisfactory responder and retention rates, demonstrating the effectiveness and tolerability of PER. No negative effects were found for cognitive function, but a nonnegligible impact on aggressive behavior was noted when compared with other ASMs. Patients with previous psychiatric comorbidities had a greater risk of psychiatric side effects under PER treatment. PER induces an overall improvement in quality of life.

Conclusions After synthesizing the study results, PER was a safe and effective choice as an additional therapy for patients with refractory epilepsy. A comprehensive evaluation of behavior and psychiatric risk is suggested before implementing PER.

Keywords antiepileptic drug; perampanel; efficacy; cognition; behavior; cognitive psychology.

INTRODUCTION

Maintaining medication compliance in patients with epilepsy requires maximizing the efficacy of and minimizing the adverse effect (AE) from antiseizure medications (ASMs). Epilepsy is a highly prevalent neurological disorder with a worldwide incidence of 67.8 per 100,000 persons.1 Seizures are caused by an imbalance between excitatory and inhibitory conductances involved in neural network activity.2 To rectify this, ASMs restore neurotransmission coordination and stop seizure initiation and propagation in order to achieve reductions in seizure frequency.

ASMs were known as the ‘magic bullet’ and treat seizure in several pathways.3 An ASM enhances inhibitory signals by modulating γ-aminobutyric acid (GABA) transmission. Sodium channels, voltage-gated calcium channels, and presynaptic vesicle glycoprotein 2A

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(SV2A) are often targeted by ASMs to attenuate the excitatory pathways. In the last decade, an increasing number of new-generation medications were approved by the Food and Drug Administration (FDA), including perampanel (PER), which is a highly selective, noncompetitive α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor antagonist.

This systematic review explores how PER affects seizure control, cognitive function, behavior, and psychiatric status in patients with epilepsy. PER was approved by the FDA in 2012 for use in the US and EU. PER is currently indicated as monotherapy or an adjunctive treatment for focal-onset seizures with or without secondary generalized seizures in patients aged 4 years and older, and as an adjunctive treatment for primary generalized tonic–clonic (PGTC) seizures in those aged 7 years and older. Preclinical studies and clinical trials have demonstrated the safety and efficacy of adjunctive PER in seizure control at dosages of 4–12 mg/day.

Cognitive, psychiatric, and behavioral alterations are common comorbidities in patients with epilepsy that can greatly affect their quality of life (QOL). These may be caused by epilepsy-related brain damage or as side effects of medications. Being acquainted with the effects of medication is therefore essential for planning therapeutic epilepsy regimens.

Neurophysiological and electrophysiological effects of PER

There are three types of ionotropic glutamate receptors: NMDA, AMPA, and kainate receptors. Among these, AMPA receptors are widely distributed in the thalamocortical tract and mediate fast excitatory neurotransmission in the propagation of seizure discharges. Glutamate activates AMPA receptors and opens sodium channels. The resulting cation influx mediates fast depolarization and promotes excitatory glutamatergic neurotransmission. Excessive excitatory postsynaptic potentials promote seizure initiation and propagation. AMPA receptor antagonists play important roles in reducing calcium influx through AMPA receptors in the subcortical regions. 

PER is an allosteric negative modulator of postsynaptic excitatory neurotransmission that increases the after-discharge threshold and duration. Reduction of motor seizure duration and seizure severity without affecting the glutamate level can be observed after administering PER. This pharmacodynamic effect also alters the electrophysiological presentation, demonstrated by the spectral power and connectivity in electroencephalography (EEG). One study analyzed the acute effect of PER in EEG activity in 17 adults and 10 children, with a 12-week follow-up after PER initiation. Quantitative EEG analysis revealed a significant increase in the beta band and a global reduction in the delta band in both children and adults. However, an opposite result has been reported for the long-term effect of PER. Quantitative EEG indicated increased theta-band power and decreased alpha-band power and theta/alpha ratio in all brain regions after 25 weeks of taking PER. A decrease in the alpha band in global connectivity measured using the weighted phase lag index was also demonstrated by another study that analyzed the spectral power of EEG after taking PER for 25 weeks. Increase in delta and theta bands in the temporal and parietal regions were also recorded in that study. These changes were not significantly correlated with total serum PER levels. However, only free-form PER can act on the central nervous system (CNS), and its strong protein-binding property might make this misleading.

Slowing of the electrophysiological system suggested a likelihood of decreased reaction times due to slight cognitive decline. Although there is evidence that the long-term effect of PER induces background EEG slowing, the phase-locking value indicated that global connectivity was not affected. The lack of a significant increase in global brain connectivity implied that epileptic discharge propagation had been avoided. Based on 10 years of clinical experience with PER, this systematic review presents the latest evidence for its efficacy in treating different seizure types and its effects on cognitive, behavioral, and psychiatric symptoms in patients with epilepsy.

METHODS

Data sources and search terms

This systematic review identified relevant clinical studies that appeared in the literature, including the PubMed and Google Scholar databases, between February 2015 and May 2021. The search terms included “perampanel,” “Fycompa,” “cognitive function,” “behavior,” “psychiatric,” “mood,” “epilepsy,” and “seizure.” Only articles published in English were included. Patients with epilepsy from different age groups or with underlying health conditions, such as intellectual disability (ID) or brain tumor, were included. No study-type restrictions were applied.

Eligibility criteria and study selection

The search identified 139 studies: 134 from PubMed and 5 from Google Scholar. After removing duplicate publications and articles without full texts, 73 studies were selected. Another 45 articles were excluded due to the lack of clarification of seizure type or relevant data related to our topic (efficacy, cognition, behavioral, and psychiatric effects), or narrative reviews and relevant data integrated by later publications. We included 28 eligible articles after performing the screening process (Fig. 1).

The selected 28 articles included 2 randomized controlled...
trials (RCTs), 1 post-hoc analysis of an RCT, 10 prospective observational studies, 11 retrospective observational studies, 1 cross-sectional study, 2 case series, and 1 case-control study (Table 1). Drug efficacy, the effects of PER on behavior and aggressiveness, the impact of PER on cognition, and the influence of PER on psychiatric status and mood were the focuses of 14, 8, 4, and 2 studies, respectively.

**Outcome measurements**
The primary outcome of interest was seizure frequency changes relative to baseline, which is a valid measurement of ASM efficacy. Secondary outcomes were the 50% responder rate (≥50% reduction in seizure frequency) and the seizure-free rate. The retention rate (proportion of participants continuing PER at study endpoints) was also used as an indicator of PER tolerability. Safety outcomes are presented as percentage of patients experiencing PER effects on cognitive, psychiatric, and behavioral symptoms, as well as other AEs.

**RESULTS**

**Efficacy and tolerability**
PER is a novel third-generation ASM, and its efficacy was evaluated using a pooled analysis of three phase III clinical trials from 2013. Decreases in the frequencies of both focal seizures and secondary generalized seizures were achieved under different PER dosages (4, 8, and 12 mg). Patients also experienced a >50% reduction in seizure frequency compared with placebo. For safety, these phase III studies found slight increases in mild-to-moderate AEs compared with the placebo group, but no deaths were recorded.

**Therapeutic efficacy of PER as early additional therapy**
The efficacy of PER as an early additional (first or second additional ASM) therapy was found in 113 patients in a prospective study in Spain. That study included patients with focal-onset seizures who were followed up for 12 months. At the end of the study, the 50% responder rate and seizure-free rates were 68.1% and 26.5%, respectively. The seizure-free rate was significantly higher in the first additional therapy group than in the second. The respective retention rate was 80.5%.

Two retrospective studies compared the efficacy and tolerability of PER with that of the SV2A modulators brivaracetam and levetiracetam (LEV). Previous studies included patients with focal-onset and general tonic-clonic seizures, whereas one more-recent study only included patients with uncontrolled secondary generalized seizures. The efficacies and tolerabilities of these three drugs were similar. Unexpectedly, the LEV group exhibited a significantly lower retention rate than the PER group after 3 and 12 months of follow-up due to there being fewer AEs in the PER group.

Investigation of the synergistic effects of ASM combinations involving PER suggested an inferior response when PER was used with concomitant sodium-channel blockers or strong enzyme-inducing ASMs such as carbamazepine or phenytoin. Since PER is primarily metabolized in the liver by cytochromes P450 3A4 and P450 3A5, concomitant P3A4 enzyme-inducing ASMs may increase clearance, thereby decreasing the efficacy of PER.

**Seizure types**

**Focal seizures**
Outcomes of patients receiving PER for treating focal seizures
Table 1. Studies finding cognitive, behavioral, and/or psychiatric adverse reactions to PER

| Study | Year | Study design, duration | Study population | Main findings |
|-------|------|------------------------|------------------|--------------|
| Liguori et al. | 2020 | Case-control study, 12 months | 107 adults with uncontrolled seizures; 64 (age 43.00±17.44 years, age range 20–80 years) used PER and 43 used BRV (age 42.32±15.78 years) as add-on | Discontinuation due to irritability in 6.2% (vs. ataxia and negative mood in 4.6% using BRV) |
| Lee et al. | 2020 | Cohort study, 6 months | 32 adults (age 42.4±10.3 years) with refractory focal seizures, using PER as add-on | Increased tendency to aggression and depression on PER. PER dose of ≥8 mg associated with aggravation. Concomitant topiramate provided protective effect |
| Liguori et al. | 2018 | Cohort study, 12 months | 41 adults with cryptogenic or symptomatic epilepsy, of which 15 (age 40.00±18.53 years) used PER and 26 (age 41.69±17.87 years) used LEV as add-on | Discontinuation due to AEs (sleepiness, irritability, depression, anxiety, and aggressiveness) less frequent with PER (2/15, 13.3%) than with LEV (9/26, 34.6%) |
| Piña-Garza et al. | 2020 | Post-hoc analysis of RCT, 4 weeks | 372 adolescents (age 12–17 years) with uncontrolled partial-onset seizures (258 on PER, 114 on placebo) | TEAEs in 74.4% using PER (vs. 66.7% with placebo), including dizziness, somnolence, and headache. Treatment discontinuation of 4.7% with PER and 4.4% with placebo |
| Abril Jaramillo et al. | 2020 | Observational cohort study, 12 months | 113 adults (mean age 40.3 years) with FOS received PER as early add-on treatment (37.2% and 62.8% as first and second add-ons, respectively) | Retention rate at 12 months was 80.5%. Seizure-free rate is higher when PER was added as first add-on. Drug-related AE rate of 30.1% |
| Santamarina et al. | 2020 | Cohort study, 12 months | 149 adolescents and adults (mean age 41 years, age range 12–84 years) with epilepsy, using PER as add-on | AEs in 48.3%, leading to PER discontinuation in 10.1%. Dizziness (15.4%), irritability (14.1%), and drowsiness (14.1%) were the most-common AEs |
| Rohracher et al. | 2018 | Observational cohort study, 12 months | 2,396 adolescents and adults (aged ≥12 years) from 45 centers in Europe (95% focal-onset seizures), using PER as add-on | 1-year retention rate of 48%; seizure-free in 9%; TEAEs were in line with previous reports (68%) |
| French et al. | 2015 | RCT, 21 weeks | 162 (81 on placebo, 81 on PER) aged ≥12 years with PGTC seizures under adjunctive PER at daily doses of 4–12 mg | 30.9% of PER-treated patients achieved PGTC seizure freedom. The most-frequent TEAEs with PER were dizziness (32.1%) and fatigue (14.8%). |
| Villanueva et al. | 2018 | Observational cohort study, 12 months | 149 adults (mean age 35.9 years) from 21 Spanish hospitals with idiopathic generalized epilepsy; mean dose 6 mg at endpoint | Retention rate at 12 months of 83.2%. Main reasons for discontinuation were lack of effectiveness and AEs |
| Maschio et al. | 2020 | Observational pilot study, 6 months | 26 patients with brain tumor-related epilepsy (mean age 47.5 years), using PER as monotherapy or in polytherapy | Vertigo or aggressiveness in 4 patients (15.4%), leading to dose reduction (n=2) or discontinuation (n=2). No difference in neuropsychology, mood, or QOL (vs. baseline). |
| Lin et al. | 2019 | Cohort study, 6 months | 44 adults (age 42.0±13.3 years) with mesial temporal epilepsy, using PER as add-on | AEs in 52.3%, leading to dose reduction in 20.5% and discontinuation in 13.3%. Dizziness (25.0%), malaise (9.1%), and irritability (6.8%) were the most common |
| Huber and Schmid | 2017 | Cohort study, 24 months | 26 patients (mean age 30 years, age range 21–55 years) with grade III drug-resistant epilepsy and cognitive deficits of various degrees, using PER as add-on | AEs (irritability, aggression, increased sensitivity, and suicidal ideation/behavior) in 50%, leading to discontinuation of PER in 42.3% |
| Andres et al. | 2017 | Cross-sectional study, 24 months | 27 adults (mean age 34 years, age range 18–51 years) with drug-resistant epilepsy and intellectual disability, using PER as add-on | 81% reported AEs, of which behavioral problems were the most prominent (n=15). 6 (2.2%) discontinued PER due to lack of efficacy or AEs |
| Lin et al. | 2018 | Cohort study, 12 months | 66 children or adolescents (age 14.9±2.3 years) with pharmacoresistant epilepsy, using PER as add-on | TEAEs in 35.7%, leading to discontinuation of PER in 12.1%. Irritability (10.6%), skin rash (9.1%), dizziness (9.1%), and somnolence (7.6%) were the most common |
| Study | Year | Study design, duration | Study population | Main findings |
|-------|------|------------------------|------------------|---------------|
| Kanemura et al\(^{31}\) | 2020 | Cohort study, 12 months | 14 adolescents (mean age 13.3 years, age range 12.1–14.3 years) with LEV-resistant epilepsy and behavioral problems, using PER in polytherapy | Hyperactivity and impulsivity improved in 6 patients. PER was more effective in patients with than without concomitant LEV (71.4% vs. 14.4%) |
| Lattanzi et al\(^{32}\) | 2021 | Cohort study, 12 months | 92 adults (aged >65) with epilepsy and different comorbidities treated by a median daily PER dose of 6 mg | Responder rate of 57.6%, and 23.9% were seizure-free. Reasons for discontinuation included insufficient efficacy (30%), AEs (60%), or both (10%). The most-common AEs were irritability and somnolence |
| Meschede et al\(^{33}\) | 2018 | Cohort study, 50.91 weeks (PER) or 59.46 weeks (LCM) | 94 adults with focal symptomatic or cryptogenic epilepsy. 57 on PER (age 43.3±11.92 years), 37 on LCM (age 40.7±14.51 years). | Significant improvement in executive and memory functions with LCM, but not with PER. No increase in self-perceived aggression, irritability, or agitation with PER (vs. baseline) |
| Rea et al\(^{34}\) | 2019 | Cohort study, 6 months | 27 patients (mean age 37.5 years, age range 20–56 years) with epilepsy, using PER as add-on | TEAEs in 67%. CNS-related AEs, including vertigo, ataxia, aggression, were the most common. Psychiatric TEAEs in 37%. No difference in cognitive functions and QOL (vs. baseline) |
| Piña-Garza et al\(^{35}\) | 2018 | RCT with an open-label extension phase, ≥52 weeks | 114 adolescents (age 14.3±1.8 years) with partial seizures who received PER (n=73) or placebo (n=41) in the prior double-blind phase and entered the extension phase | No negative effect on the global cognition score, but was associated with a significant decline in attentional power at endpoint |
| Oporto et al\(^{36}\) | 2020 | Cohort study, 12 months | 37 adolescents (age 13.7±160 years) with focal drug-resistant epilepsy | No negative effect on executive function, emotion, or behavior with PER, but 5 patients (13.9%) discontinued PER due to dizziness and headache |
| Goji and Kanemoto\(^{37}\) | 2019 | Cohort study, 12 weeks | 59 adults (age 35.3±13.3 years, age range 18–70 years) with epilepsy, using PER as add-on | Significant worsening of total aggression scores and no difference in hostility after treatment with PER. Depression reported in 23.7% at endpoint |
| Juhl and Rubboli\(^{38}\) | 2017 | Case series, 6 months | 12 adults (mean age 44 years, age range 25–67 years) with severe drug-resistant focal epilepsy, using PER as add-on | 12 patients experienced aggression (24.5%). 10 of the 12 patients discontinued PER due to aggressive behavior |
| von Wrede et al\(^{39}\) | 2021 | Self-report study | 68 patients with epilepsy using PER (n=33) or LEV (n=35) | 36% experienced negative behavioral changes (vs. 38% with LEV). LEV significantly worsened scores for cognition, mood, and physical domains, while PER only affected the mood domain |
| Hasegawa and Tohyama\(^{40}\) | 2021 | Case–control study | 98 adults (age 44.5±14.6 years) with epilepsy who had been treated with LEV and PER | Irritability in 17.3% on PER vs. 7.1% on LEV |
| Youn et al\(^{41}\) | 2018 | Cohort study, 3 months | 81 patients (age: median: 17; maximum, minimum, interquartile range: 32, 12, 14–20) | AEs in 58%, leading to PER discontinuation in 15%. Dizziness (37%), aggressive mood and behavior (24%), gait disturbance (20%), and sleep problems (12.4%) |
| Moraes et al\(^{42}\) | 2020 | Nested cohort study, 12 months | 160 adolescents and adults (age ≥16 years) with drug-refractory focal epilepsy using PER as monotherapy or add-on | In the retrospective cohort, mood changes (7.6%), depression (4.3%), and irritability (6.5%) were the most common |
| Ahn et al\(^{43}\) | 2021 | Cohort study, 25 weeks | 17 adults (age 32.6±12.2 years) with epilepsy using PER | Memory improved with PER, but negative effect on cognition as evaluated using EEG |
| Stephen et al\(^{44}\) | 2017 | Cohort study, 6 months | 1,058 adults (median age 45 years), 54 patients in PER group; all patients with focal-onset epilepsy | 16.7% discontinued PER use due to psychiatric side effects including depression, irritable mood, and anxiety, which is a higher rate than for other ASMs |

Data are mean±SD values except where indicated otherwise.

AE, adverse event; ASM, antiseizure medication; BRV, brivaracetam; CNS, central nervous system; EEG, electroencephalography; FOS, focal-onset seizures; LCM, lacosamide; LEV, levetiracetam; PER, perampanel; PGTC, primary generalized tonic–clonic; QOL, quality of life; RCT, randomized controlled trial; TEAE, treatment-emergent adverse event.
were found among 2,396 patients (95% with focal-onset seizures with or without secondary generalization) aged ≥12 years in a pooled observational study. Data were collected from 45 centers in Europe during 2009–2016. After 1-year of follow-up, the reported retention rate was 48% and seizure-free rate (at least 6 months) was 9.2%. The 50% responder rates at 3, 6, and 12 months were 42%, 46%, and 39%, respectively. AEIs were reported by 68% of patients, and intolerability was the main reason for discontinuing medication.

PGTC seizures
AMPA receptors are one of the therapeutic targets when treating PGTC seizures. Outcomes for patients with drug-resistant PGTC seizures associated with idiopathic generalized epilepsy (IGE) were found in an RCT with 21 weeks of follow-up. Encouraging 50% responder (64.2%) and seizure-free (30.9%) rates were reported in 81 patients that received PER, which were both significantly higher than those in the placebo group (n=82). The retention rate was 84%, and AEs such as dizziness and fatigue were the most-common reasons for medication discontinuation.

A retrospective observational study explored the outcomes of patient with generalized tonic-clonic seizures (GTCS) and other seizure types who received PER to treat idiopathic IGE. After 12 months of follow-up, 149 participants demonstrated an 83% retention rate. The seizure-free rate was 59% for all seizures (n=88) and 63% for GTCS, and the 50% responder rate for GTCS was 75.7%. However, 5.2% of patients with GTCS reported increased seizure frequencies and 50% had mild-to-moderate AEs.

Refractory epilepsy
Refractory epilepsy, defined as frequent recurrent seizures in patients taking at least two ASMs, affects 20%–40% of patients with epilepsy. Seizure control is more difficult to achieve in patients with symptomatic epilepsy even when applying polytherapy.

A 6-month longitudinal study included 32 adults with refractory focal epilepsy. In that study, the mean number of baseline concomitant ASMs was 3.2 (SD=0.9), and 37.5% of patients reached the ≥50% responder rate and retention rates of 76.3% were reported at the end of the study under additional PER at a mean daily dosage of 6.0 mg (SD=1.8 mg).

Brain-tumor-related refractory epilepsy
Brain-tumor-related epileptogenesis is associated with elevated glutamate and with the lack of glutamate stability in the CNS. Reducing AMPA receptor activity would be an effective strategy to control seizures.

Maschio et al. enrolled 26 patients with brain-tumor-related epilepsy in a pilot observational study. Promising results were observed after 6 months of PER administration, including 57.8% of patients achieving a 50% seizure reduction rate and 30.6% seizure-free rate.

Mesial temporal lobe epilepsy (MTLE)–related refractory epilepsy
Lin et al. reported a 46.9% responder rate at a 6-month follow-up in patients receiving PER therapy for MTLE and hippocampal sclerosis. Among the patients, 11.3% obtained complete seizure-free status during the study period, although half of the patients experienced mild-to-moderate AEs.

Patients with ID
Individuals with ID are often excluded from regulatory RCTs due to poor medication compliance or a high discontinuation rate. However, patients with ID account for a considerable proportion of the intractable epilepsy population. A retrospective study that exclusively recruited 26 patients with ID found responder rates (≥50% seizure reduction) after 6, 12, and 24 months of 11.5%, 23.1%, and 7.7%, respectively, and retention rates of 61.5%, 46.2%, and 42.3%.

Another cross-sectional retrospective study found a 2-year retention rate of only 28% in 27 patients with ID of different degrees. Poor adherence is mostly caused by intolerable psychiatric AEs, including irritability, aggression, and increased sensitivity. Suicidal ideation was the most-frequent reason for discontinuation.

Age group

Children or adolescents
Adolescent and adult patients have somewhat consistent efficacy outcomes. A post-hoc analysis of six phase II and III studies demonstrated a satisfactory efficacy and tolerability of additional PER compared with placebo regardless of seizure type in adolescent patients (aged 12–17 years). A cohort study of 70 Asian children or adolescents with pharmaco-resistant epilepsy aged 8–18 years included patients with different seizure types (focal or generalized tonic–clonic, myoclonic, or spasm seizures). The overall responder and retention rates were 34.7% and 51% after 1 year of follow-up, respectively. Inadequate efficacy and intolerable AEs were the most-common reasons for discontinuation. Notably, one patient with Lennox–Gastaut syndrome and one with intractable juvenile myoclonic epilepsy were both free from seizures for 23 and 12 weeks, respectively.

Apart from the clinical outcome, interictal paroxysmal epileptic discharge on EEG is another crucial indicator for outcome measurement. A 12-month prospective study included
14 adolescents with intractable epilepsy and insufficient responses to LEV. All patients presented with secondary bilateral synchrony (SBS) in EEG, which may be relevant to a cognitive decline and behavioral problems. Eight patients (57.1%) were considered clinical responders and six (42.9%) as both clinical and EEG responders after 12 months of follow-up. These six EEG responders also achieved improvements in hyperactivity and impulsivity according to the Aberrant Behavior Checklist (ABC). Seven patients had insufficient responses to LEV, of which five (71.4%) were considered responders after PER use.

Additional attention is needed for teenage patients because of their reported high prevalence of epileptic syndrome. Appropriate ASMs need to be selected to ensure good responses.

Elderly patients
The incidence rate of epilepsy surges among older adults, and their comorbidities pose a challenge to its management. Impaired liver or renal function and comedication interactions may alter the pharmacokinetics and lead to unpredictable outcomes. A thorough assessment of the efficacy and tolerability of PER in elderly patients is therefore helpful in making treatment decisions.

One study assessed 92 patients older than 65 years with both focal and generalized onset seizures who received additional PER therapy. The most common etiology of epilepsy was caused by structural lesion. In that study, 23.9% of patients became free from seizures and 57.6% experienced a 50% seizure reduction after 12 months, and the retention rate was 78.3%. Insufficient efficacy and AEs were the fundamental causes of medication discontinuation. In summary, PER adjunctive treatment provided a safe and effective option for elderly patients with epilepsy.

Effect on cognition
Cognitive dysfunction is common in patients with epilepsy. The increased vulnerability is attributed to changes in cerebral structure and function. Adjunctive PER did not have a significant influence on global cognitive profiles.

Subanalyses of cognitive profile in different domains
Adjunctive PER therapy outcomes in different domains of cognitive functions were evaluated in 27 patients who underwent extensive neuropsychological testing at baseline and after 6 months of medication use. The Rey Auditory Verbal Learning Test revealed a significant improvement in verbal memory of the nonresponder group, whereas other domains (attention, frontal lobe function, executive function, and logical-abstract thinking) remained unchanged at the endpoint in both the responder and nonresponder groups. PER was found to have no negative influence on attention and executive function in two retrospective cohort studies. In a comparison with lacosamide, PER scored lower on the neuropsychological effects EpiTrack test and a verbal learning and memory test at the follow-up. These findings indicated that lacosamide exerted better effects on executive function and verbal memory than did PER.

Cognitive effects of PER in adolescents
Regarding the long-term cognitive effects of PER in adolescent patients, current evidence indicates no differences after taking PER compared with baseline. The extension phase of a randomized controlled study followed up on 114 adolescents with pharmacoresistant epilepsy aged 12–18 years for 52 weeks. PER had no effect on Clinical Dementia Rating global cognition scores except for a decline in the power of the attention subdomain. Language and manual dexterity skills remained unchanged compared with baseline. PER was not associated with growth or development (in terms of changes in weight or height).

Behavioral effects
“Serious psychiatric and behavioral adverse reactions” is stated in the warning box on the PER label. Aggressiveness and irritability are the psychiatric AEs of greatest concern.

Researchers have analyzed the association between aggressive behavior and additional PER use. A short-term (12-week) observational study used the Buss-Perry Aggression Questionnaire (BAQ) to assess aggressive behavior in 59 patients after they were first administered PER. The total BAQ score at the endpoint increased significant, especially in verbal and physical aggression, regardless of concomitant ASM. However, this change may have been underestimated due to the short observation period. Another prospective cohort study found a deteriorative trend measured using the Korean version of the Aggression Questionnaire (AQ-K) at a 6-month follow-up. Depression and PER doses ≥8 mg were predictors of aggression behavior exacerbation. Surprisingly, combination therapy with low-dose topiramate (25–50 mg) and PER provided a protective effect based on AQ-K scores.

Intolerable PER-related aggressiveness, chiefly verbal and behavioral, was found in 20% of patients with severe drug-resistant focal epilepsy. Its symptoms can occur immediately after treatment initiation, but may also occur after as long as 20 months. One-third of these patients received a relatively low dosage (2–4 mg/day). This result was inconsistent with previous dose-dependent theories of behavioral effects. Also, 41% of patients developed aggressiveness while taking LEV, which suggests that the pharmacodynamic inhibition of glutamatergic transmission by LEV and PER plays a crucial role.
Behavioral effects in adolescents
In premarketing studies, the overall rates of aggression AEs were 3.1% and 8% in adolescents. Unlike results for the general population, current evidence does not indicate a negative influence on behavior. Surprisingly, PER therapy may be associated with a positive influence on behavior.

A study investigating behavioral problems for teenage patients with epilepsy and SBS patterns in EEG found significant improvements in scores for the Japanese version of the ABC, especially for hyperactivity and impulsivity, after 12 months of PER administration in EEG responders (>50% reduction in SBS on EEG). Another study that focused on adolescent patients with focal epilepsy also demonstrated no negative influence on behavioral problems at a 12-month follow-up. Adolescents with drug-resistant epilepsy appeared to be more vulnerable to ASM-related behavioral effects. The effects were dose-dependent, and having an underlying psychiatric condition was an essential risk factor.

Behavioral effects of PER in patients with ID
Behavior deterioration tends to occur in only 7% of the PER-treated population. However, a cross-sectional study found that behavior changes occurred in 55% of patients with ID at a 12-month follow-up. That study recruited 27 adults with intractable epilepsy and ID who were receiving additional PER. The retention rate was 28% after 24 months in patients with ID, of which 8 patients (30%) discontinued medication use due to aggression development, which at a mean dosage of 6.9 mg/day led to self-injury and injurious behaviors toward others. The Aggressive Behavior Scale indicated deterioration in 73% of patients after 24 months of PER administration.

The underlying mechanism of aggressive behavior is still not clear. It could be related to the poor expression of other AEs or be classified as a release phenomenon after obtaining seizure control in patients with ID. Despite the fair level of efficacy noted for PER in patients with ID, tolerability should also be considered before prescribing PER for such patients.

Psychiatric effects of PER
The prevalence rates of psychiatric disorders, mostly depression and anxiety, are much higher in patients with epilepsy, especially in treatment-resistant patients. Mood disorder was reported in 2.4% of patients who received PER at 12 mg/day, but such a change was not observed for PER at 4 mg/day and in a placebo group, implying a dose-dependent effect.

A nested prospective cohort study evaluated the effect of adjunctive PER on mood. Overall improvements in mean scores for QOL and mood were observed at 6- and 12-month follow-ups. In that study, 7 of the 59 patients (11.9%) had significant worsened depression according to Neurological Disorders Depression Inventory for Epilepsy (NDDI-E) scores at the end of follow-up. Higher baseline NDDI-E scores are significantly correlated with greater deterioration.

A retrospective study that investigated the association between psychiatric side effects and ASM withdrawal in patients with treated epilepsy. That study included 1,058 patients treated with 8 different new-generation ASMs. Among all patients, 1.9% to 16.7% discontinued ASMs due to neuropsychiatric AEs, with the proportion being highest in the PER group. Depression and irritable mood were the most commonly mentioned side effects.

Quality of life
Epilepsy markedly affects the physical, mental, and social well-being of affected patients. The effect of ASM is one of the key contributors impacting QOL. The beneficial effect of PER has been demonstrated in several studies.

A nested prospective cohort study included 160 patients with drug-resistant epilepsy to evaluate the influences of PER on QOL. PER was associated with a 30.6% responder rate and 9.4% seizure-free rate after 6 months. A more-stable psychiatric and behavior manifestation was indicated by significant increases in mean Patient Weighted Quality of Life in Epilepsy scores. The comprehensive improvement explains the foremost enhancement in QOL and the high retention rate (68%) at the end of that study.

DISCUSSION
The present systematic review has summarized the efficacy and the cognitive, psychiatric, and behavioral effects of PER. PER is an antagonist for the glutamate AMPA postsynaptic receptor and its unique mechanism is believed to be attributable to it being a therapeutic target in both focal-onset and PGTC seizures. Among all included studies, promising efficacy was clinically demonstrated across seizure types and age groups of patients. For drug-resistant patients, studies have also demonstrated the effectiveness of PER in symptomatic epilepsy. Responder and seizure-free rates have varied widely across studies, with PER being found to offer benefits in about 10%-30% of these patients.

Tolerability is as important as efficacy in managing refractory epilepsy. More than 50% of patients experienced mild-to-moderate AEs with PER treatment, with dizziness and fatigue being the most common. Nevertheless, effects on cognitive function, and psychiatric and behavior deterioration have raised concerns among PER recipients. Irritability,
aggression, and suicidal ideation are the most-common reasons for discontinuing its use. Although the pathogenesis is not well understood, AMPA-receptor-blockade-related subcortical network dysregulation involving GABA and the serotonin system may account for the adverse psychiatric and behavioral reactions.\textsuperscript{12} Complete evaluation of the psychiatric status is recommended for patients with psychiatric comorbidities before prescribing, dosing, and titrating PER.\textsuperscript{27}

The current evidence indicates that PER does not negatively affect cognitive function in the general population or in adolescent patients receiving PER. Subanalyses of different domains demonstrated potential improvements in verbal memory but a decline in attentional power in adolescents.\textsuperscript{34,35} These outcomes should encourage neurologists to prescribe PER to patients who are vulnerable to cognitive deterioration.

The side effects of aggressiveness and irritability appear to require extra attention.\textsuperscript{28,31,37,39} Patients with underlying psychiatric and behavioral comorbidities (anger or aggression) are particularly vulnerable to worsening of their psychiatric condition. Rapid titration and high dosages of PER should be avoided in order to prevent further deterioration.\textsuperscript{42} The association between psychiatric effects and PER therapy is still debated. Patients with a previous comorbid mood disorder, such as anxiety and depression, also require regular detailed assessments.\textsuperscript{41} The complex and multifactorial background poses a major challenge in differentiating the non-ASM-related causes.

Despite some concerns as detailed above, a beneficial effect in improving QOL has been found in several studies. The overall retention rates were around 70\%-80\% across the studies included in the present review, suggesting that PER is a safe and effective option when patients are selected carefully.

Epilepsy is a disabling disease that often results in patients being emotionally and physically disturbed. Neurologists are striving to solve these issues by establishing effective and tolerable therapeutic regimens. The current synthesis of current real-world data among 28 studies indicated that PER was safe and effective as an antiepileptic agent administered to patients with epilepsy. PER reduces the seizure frequency and achieves satisfactory responder and retention rates, even though patients with previous psychiatric comorbidities are at a greater risk of psychiatric side effects under PER treatment. Comprehensive behavior and psychiatric risk assessments are suggested before administering PER. Further studies exploring the association between PER therapy and the mechanisms of psychiatric and cognitive effects are needed to provide more information and a better understanding of the PER profile.

**Availability of Data and Material**

The datasets generated or analyzed during the study are available from the corresponding author on reasonable request.

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**Conflicts of Interest**

The authors have no potential conflicts of interest to disclose.

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