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Beyond Clinical Trials: Perampanel across the Lifespan in Contemporary Epilepsy Practice

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Introduction

Perampanel (PER) occupies a singular place in anti-seizure pharmacology. As the only anti-seizure medication (ASM) that acts through selective, non-competitive blockade of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors, the principal mediators of fast excitatory neurotransmission in the brain, it brings a mechanistic distinctiveness that sets it apart from agents targeting sodium channels, calcium currents, or synaptic vesicle proteins [1,2]. While its unique mechanism of action initially generated considerable interest, its clinical value has ultimately been established through a decade of accumulating real-world evidence rather than pharmacological novelty alone.

The original registration trials established efficacy in refractory focal-onset seizures and defined a tolerability profile associated with primarily dizziness and somnolence [3–5]. Subsequent Phase 3 trials extended this evidence base to generalized tonic-clonic seizures [6] and to pediatric populations through an open-label study [7]. These pivotal studies, however, were designed to meet regulatory thresholds rather than to reflect the complexity of everyday clinical practice. Key questions remained unanswered: How durable is treatment response over time? Does effectiveness vary meaningfully across age groups? How does PER perform in patients with psychiatric and cognitive comorbidities, conditions that are consistently underrepresented in randomized trials?

Two major real-world studies, the PERMIT pooled analysis of 44 clinical-practice cohorts across 17 countries [8] and the United States-based Phase 4 PROVE study [9], have evaluated the effectiveness, safety, and tolerability of PER in routine clinical care. The PERMIT Extension study combines these datasets, encompassing nearly 7,000 patients, and represents the largest pooled analysis of PER use in focal and generalized epilepsy conducted to date [10]. By evaluating PER across the full heterogeneity of routine care, PERMIT Extension provides insights that traditional registration trials cannot capture and offers a more accurate picture of how the drug performs in the patients clinicians actually treat. A summary of pivotal trials, major real-world studies, and key evidence syntheses are summarized in **Table 1**.

Broadening the Therapeutic Horizon

A true broad-spectrum agent

Approximately 10 to 15% of individuals with idiopathic generalized epilepsy (IGE) develop drug-resistant epilepsy (DRE) [11]. Furthermore, among adults with IGE, drug-resistant seizures occur in up to one-third of patients depending on age of onset and subtype, a proportion comparable to that seen in focal epilepsy [12–14]. Despite accounting for approximately 20% of the overall epilepsy burden, IGE receives fewer than 1% of epilepsy-related scientific publications, owing in part to limited awareness of DRE in this population [14]. There is therefore a pressing need to evaluate newer therapeutic options in IGE, particularly for patients with DRE. One of the most consequential developments in PER literature is the growing body of evidence supporting broad-spectrum efficacy. Although early trials focused exclusively on focal epilepsies [3,4], a subsequent randomized controlled trial in generalized tonic-clonic seizures, combined with real-world data, now consistently demonstrate robust effectiveness across generalized seizure types [10,15]. Notably, the PERMIT Extension study demonstrated that both responder and seizure-freedom rates were consistently higher for generalized seizures than for focal seizures [10]. This pattern has been corroborated by multiple independent analyses [7,15], positioning PER as a compelling therapeutic option for this population.

Table 1. Evolution of the perampanel evidence base: pivotal trials, major real-world studies, and key evidence syntheses*.

Study	Population	Design	Key Efficacy Findings	Retention	Key Safety/ Tolerability Findings
Pivotal Trials					
French *et al*. 2012 (Study 304) [3]	Refractory focal epilepsy	Phase III RCT	Significant improvement in responder rates vs placebo	NR	Dizziness, somnolence, fatigue most common AEs
French *et al*. 2013 (Study 305) [4]	Refractory focal epilepsy	Phase III RCT	Significant seizure reduction with PER 8–12 mg	NR	Dose-related neurological and behavioral AEs
Krauss *et al*. 2012 (Study 306) [5]	Refractory focal epilepsy	Phase III RCT	Significant reduction in seizure frequency	NR	Generally well tolerated; dizziness most frequent AE
French *et al*. 2015 [6]	Idiopathic generalized epilepsy with GTCS	Phase III RCT	64.2% responder rate vs 39.5% with placebo; significant reduction in GTCS frequency	NR	Safety profile consistent with focal epilepsy studies
Fogarasi *et al*. 2020 [7]	Children aged 4–<12 years	Open-label pediatric study	Clinically meaningful seizure reduction across seizure types	High study completion	No new pediatric safety signals
Major Real-World Studies					
PERMIT (Villanueva *et al*. 2022) [8]	5,190 patients with focal and generalized epilepsies	Global pooled real-world analysis	58.5% achieved ≥ 50% seizure reduction; 23.6% seizure freedom	67.6% at 12 months	AEs in 37.4%; behavioral AEs generally manageable
PROVE (Wechsler *et al*. 2022) [9]	Real-world epilepsy population	Retrospective Phase IV study	Effectiveness demonstrated across focal and generalized epilepsies	Similar to other real-world cohorts	No unexpected safety findings
PERMIT Extension (Wheless *et al*. 2023) [10]	Focal and generalized epilepsies across age groups	Real-world extension study	Effectiveness maintained across age groups	~60% at 12 months	Psychiatric AEs ~20%; higher discontinuation in younger patients and those with psychiatric comorbidity
ELEVATE (Punia *et al*. 2024) [24]	Monotherapy or first adjunctive therapy	Phase IV open-label study	78.7% responder rate overall; 85.7% in monotherapy subgroup	High treatment persistence	Favorable tolerability in early-line treatment
Key Evidence Syntheses					
Fan *et al*. 2023 [30]	Real-world epilepsy studies	Systematic review/ meta-analysis	Confirmed effectiveness across diverse populations	Retention generally 54–77% in adults and 65–77% in children	Safety profile consistent with individual real-world studies
Sun *et al*. 2023 [25]	Children and adolescents	Systematic review/ meta-analysis	Demonstrated efficacy and acceptable tolerability in pediatric populations	NR	No new safety concerns identified
Kumar *et al*. 2025 [33]	Lennox–Gastaut syndrome	GRADE-assessed systematic review/ meta-analysis	50% responder rates ranging from 26–69%; seizure freedom approaching 10%	NR	Behavioral AEs more common than in broader epilepsy populations
Alyazidi *et al*. 2024 [43]	Dravet syndrome	Scoping review	Evidence suggests meaningful seizure reduction and improved quality of life	NR	Behavioral AEs and variable treatment response warrant individualized management

* Summary of pivotal clinical trials and selected real-world studies evaluating the efficacy and safety of perampanel. This table highlights key studies and is not intended to provide an exhaustive review of all available evidence.

AE: Adverse Effects; NR: No Retention assessed; RCT: Randomized Controlled Trial.

Timing of initiation and concomitant ASMs

It is well established that early response to ASM is strongly associated with improved long-term prognosis in epilepsy [16], whereas failure of two or more ASMs markedly reduces the likelihood of achieving seizure control with subsequent therapies [17,18]. As polytherapy increases the risk of adverse effects (AEs), drug interactions, psychiatric and behavioral complications, and reduced quality of life [19–22], emerging evidence suggests that PER may be associated with higher response rates when introduced earlier in the treatment course. In an exploratory post hoc analysis of all individuals included in the PERMIT Extension, the number of prior ASMs was inversely associated with PER retention, treatment response, and seizure freedom, suggesting greater effectiveness when PER is introduced earlier in the treatment course [23]. However, in this cohort, patients were taking a median of two concomitant ASMs, and PER was initiated as monotherapy in only 6.6% of participants [10]. Consequently, the ability to assess the impact of early initiation or monotherapy use is limited, and these findings should be interpreted cautiously.

The ELEVATE study extends this evidence into early-line therapy. The reported 50% responder rate of 78.7%, and 85.7% in the monotherapy subgroup, compares favorably with outcomes reported in more treatment-resistant populations [24]. However, the study was small, open-label, and lacked a comparator arm, limiting conclusions regarding the comparative effectiveness of early versus later PER initiation. Therefore, while these findings suggest that PER may be effective when used earlier in treatment, they require confirmation in larger controlled studies.

Regarding concomitant ASMs with PER, the PERMIT Extension post-hoc analysis demonstrated that response and seizure freedom were significantly less likely in individuals receiving concomitant sodium channel–blocking or GABAergic ASMs, likely reflecting reduced PER exposure due to enzyme-inducing properties of agents such as carbamazepine, phenytoin, and phenobarbital [23]. These associations may also indicate greater underlying treatment refractoriness in patients requiring these concomitant therapies, rather than a direct pharmacodynamic interaction alone. Importantly, these findings arise from a heterogeneous real-world cohort spanning diverse epilepsy types, ages, seizure profiles, and ASM regimens, and should therefore be considered preliminary pending confirmation in more targeted prospective studies.

PER across the lifespan: age-dependent benefits and risks

The PERMIT Extension's lifespan design provides a comprehensive view of how PER performs across different age groups. Most participants were adults aged 18–64 years (81.1%), with smaller proportions of children <12 years (4.5%), adolescents 12–17 years (8.4%), and older adults ≥65 years (5.9%) [10]. Older adults (> 65 years) achieved some of the highest responder and seizure-freedom rates, likely reflecting the pharmacosensitivity of late-onset epilepsies and the use of lower starting doses with slower titration. At the same time, they experienced the highest rates of AEs and discontinuation, consistent with the greater clinical impact of dizziness, gait instability, and falls in this population [10]. These findings reinforce established geriatric principles: start low, go slow, and prioritize fall-risk mitigation.

Pediatric outcomes in the PERMIT Extension revealed total seizure responder rates at 12 months were 52.6% (10/19) in children younger than 12 years and 62.0% in adolescents aged 12 to under 18, with corresponding seizure-freedom rates of 15.8% and 24.6%, respectively [10]. These figures are consistent with other meta-analytic estimates reporting responder rates of approximately 50% and seizure-freedom rates of approximately 20% across pediatric cohorts [25], rising to a 55% responder rate and 29% seizure-freedom in studies with at least one year of follow-up [26]. Efficacy in the adolescent population is further supported by a meta-analysis of three randomized controlled trials, which found that PER was associated with a significantly greater reduction in seizure frequency compared with placebo (OR 2.49) [27]. The tolerability profile in younger patients is similarly well characterized. Dizziness, somnolence, and behavioral effects are the most frequently reported AEs across pediatric cohorts, and slow titration consistently emerges as a modifiable factor that improves both tolerability and treatment response [26,28,29].

Retention

Retention, an integrated measure of efficacy, tolerability, and patient acceptability, provides an important real-world benchmark. The PERMIT Extension's 12-month retention of approximately 60% [10] closely mirrors the 63% retention observed in subsequent studies, including the prospective ELEVATE study [24] and the 65–77% (children) and 54–77% (adults) ranges reported in the Fan *et al*. meta-analysis [30]. These convergent findings across methodologies strengthen confidence in PER's long-term clinical utility.

Although the overall incidence of AEs in PERMIT Extension (49%) was lower than in clinical trials (62–92%), discontinuation due to AEs was higher (18% vs. 3–19%), likely reflecting the much longer follow-up period in real-world practice compared with the 17–19-week duration of registration trials [3–7]. Individualized dosing and titration strategies used in clinical practice appear to mitigate tolerability challenges despite the greater heterogeneity of real-world patients.

Age-stratified analyses reveal additional nuances. Retention was highest in adults aged 18–65 years and lowest in children <12 years [10]. Interestingly, psychiatric AE rates were relatively consistent across age groups (18.9–22.2%) [10], suggesting that age alone does not determine psychiatric vulnerability. Yet younger patients, particularly children and adolescents, had higher discontinuation rates despite older adults experiencing more AEs overall. This pattern possibly reflects the nature rather than the number of AEs, as behavioral symptoms such as irritability, aggression, and agitation are more disruptive in younger patients, prompting earlier discontinuation by families and clinicians. In addition, children may have less physiological reserve for dizziness or gait disturbance, and concerns related to school functioning, caregiver burden, and developmental impact often lower the threshold for stopping a medication. These factors together may explain why discontinuation rates were higher in younger patients even though older adults reported more AEs.

Neuropsychiatric and Cognitive Tolerability: A More Precise Risk Profile

Neuropsychiatric AEs remain the most closely scrutinized aspect of PER's safety profile. In the PERMIT Extension study, approximately one in five patients experienced a psychiatric AEs, a higher rate than reported in registration trials, likely reflecting the inclusion of patients with pre-existing psychiatric comorbidities who are routinely excluded from clinical studies [31,32]. Nearly one-quarter of participants had baseline psychiatric conditions, most commonly depression and anxiety, which may have contributed to the observed AE rates [10].

The study also provides important insights into age-related risk. Although psychiatric comorbidities increased with age, from 13% in children <12 years to 27% in adults ≥65 years, the incidence of psychiatric AEs remained relatively consistent across age groups (19–22%) [10]. However, adolescents demonstrated higher rates of treatment discontinuation due to aggression and behavioral disturbances, highlighting a subgroup that may require particularly close monitoring [10].

Behavioral AEs appear especially relevant in Lennox–Gastaut syndrome (LGS) and other developmental and epileptic encephalopathies (DEEs). A recent meta-analysis reported irritability in 13.7%, aggression in 11.4%, and broader behavioral change in 24.7% of patients with LGS, with more than 10% discontinuing treatment because of behavioral AEs [33]. These rates exceed those reported in broader epilepsy populations and underscore the heightened vulnerability of patients with DEEs.

Several modifiable risk factors for psychiatric AEs have been identified, including higher PER doses, rapid titration, and pre-existing psychiatric disorders [15,23]. Patients with baseline psychiatric comorbidity are more likely to experience psychiatric AEs and discontinue treatment, with risk appearing greatest at doses of 8–12 mg/day [23,34,35]. Importantly, behavioral symptoms are often reversible and may improve following dose reduction or discontinuation [23,29,34,36]. Additional factors associated with poorer tolerability include older age, longer epilepsy duration, and greater prior ASM exposure, likely reflecting increased polypharmacy, comorbidity burden, and drug–drug interactions [10,23].

From a practical standpoint, psychiatric history should be routinely assessed before initiating PER. A slow, individualized titration strategy, particularly in adolescents, patients with DEEs and LGS, those receiving polytherapy, and individuals with pre-existing psychiatric disorders, may improve tolerability. Caregivers should be counselled regarding potential mood and behavioral changes, and regular behavioral monitoring should be considered, especially during titration and after dose escalation. Early recognition of emerging symptoms may permit dose adjustment before treatment discontinuation becomes necessary.

A key distinction emerging from literature is the separation of behavioral effects from cognitive toxicity. Scorrano *et al*. found no evidence of global cognitive impairment and even observed slight improvements in verbal memory, although attentional decline was noted [28]. This supports balanced clinical counseling: cognitive function is generally preserved, but behavioral monitoring, particularly after dose escalations, remains essential. Controlled data reinforce this cognitive-behavioral distinction. In a randomized, double-blind study of healthy volunteers, PER 4 mg/day did not significantly affect overall cognitive or behavioral performance compared with baseline [37]. Only minimal changes were detected on 2 of 19 neuropsychological measures, suggesting that PER at therapeutic doses is broadly cognitively neutral with few neuropsychological AEs. Notably, 4 mg was the median dose in PERMIT Extension.

Remaining Evidence Gaps

Head to head ASM data

Despite the substantial expansion of the PER evidence base, several important knowledge gaps remain. A clear understanding of these limitations is essential for interpreting current data and guiding future research.

The most pressing gap is the near-total absence of direct head-to-head comparative trials. Clinicians choosing among modern ASMs, including PER, brivaracetam, cenobamate, lacosamide, and cannabidiol have abundant placebo-controlled trial data but almost no prospective direct comparisons, forcing reliance on cross-trial inference prone to bias from differences in study populations, background

therapies, and outcome definitions. Prospective head-to-head studies are also inherently difficult to conduct in drug-resistant populations, given ethical barriers to randomization and the practical challenges of long-term blinded follow-up. A notable exception is a recent randomized controlled trial in post-stroke epilepsy, where PER monotherapy demonstrated non-inferiority to oxcarbazepine in seizure control, retention, and tolerability over six months, providing rare prospective comparative evidence in a defined clinical context [38].

For the broader drug-resistant population, comparative data remain largely retrospective. In a multicenter pooled analysis of four retrospective studies, cenobamate demonstrated superior effectiveness, higher responder rates, greater seizure freedom, and better 12-month retention compared with brivaracetam, lacosamide, and PER, despite more AEs [39]. However informative, such pooled retrospective designs cannot establish causality, as would a prospective randomized head-to-head trial.

Specific epilepsy syndromes and DEE

While the PERMIT Extension examined outcomes according to seizure type and age, evidence supporting the use of PER in specific epilepsy syndromes and DEEs remains comparatively limited. Most syndrome-specific data are derived from observational studies, retrospective cohorts, and evidence syntheses, with relatively few randomized controlled trials available.

Among DEEs, the strongest evidence currently exists for LGS, although important limitations remain. A recent GRADE-assessed systematic review and meta-analysis identified PER as one of the more extensively studied newer ASMs in LGS, with responder rates ranging from 26% to 69% across predominantly observational studies [40]. Similarly, an updated review of pharmacotherapies for LGS concluded that PER has demonstrated consistent efficacy signals in uncontrolled studies, with reported responder rates ranging from 26.4% to 69.2% [40]. However, the overall quality of evidence remains modest because most available data originate from retrospective or open-label investigations.

Importantly, the only Phase 3 randomized trial of adjunctive PER in patients aged two years and older with LGS did not achieve statistical significance for its prespecified primary endpoint of drop seizure reduction, although significant reductions were observed for countable motor seizures and efficacy appeared to be maintained during long-term follow-up [41]. The study was terminated early, limiting statistical power and complicating interpretation of the results. Taken together, current evidence suggests that PER may represent a useful treatment option in LGS, but its role remains less firmly established than for approved indications, and additional adequately powered controlled studies are needed.

Evidence in Dravet syndrome is even more limited and relies largely on real-world experience. A recent prospective study of 21 children with Dravet syndrome reported ≥50% seizure reduction in 52.4% and 47.6% of patients at 3 and 6 months, respectively, with a 6-month retention rate of 90.5%. AEs occurred in 38.1% of patients and were generally mild and transient, with no treatment discontinuations due to AEs [42]. A recent scoping review similarly concluded that PER appears to be a promising adjunctive treatment for Dravet syndrome, with reported reductions in seizure frequency and improvements in quality of life. However, the review emphasized that the available evidence is almost entirely observational, treatment response is variable, and important questions remain regarding optimal dosing, long-term effectiveness, and patient selection [43].

Beyond LGS and Dravet syndrome, syndrome-specific evidence is sparse. Data for genetic disorders such as *CDKL5* deficiency disorder, *SCN8A*-related epilepsy, and other DEEs remain limited [44], and evidence for neonatal seizures is insufficient to support routine use. In a pediatric cohort with presumed genetic epilepsies, PER achieved a responder rate of approximately 50%, with some indication of more favorable outcomes in *SCN1A*-related epilepsies compared with other etiologies, whereas developmental delay was associated with poorer response [44].

Overall, available studies suggest that clinically meaningful seizure reduction may be achievable with PER across a range of severe epilepsy syndromes and DEEs. Yet the evidence base is characterized by small sample sizes, substantial syndrome heterogeneity, wide confidence intervals, and a predominance of observational designs. As a result, conclusions about comparative effectiveness and optimal placement within syndrome-specific treatment algorithms remain tentative. Prospective, syndrome-targeted studies incorporating standardized efficacy metrics, quality-of-life outcomes, and caregiver-reported assessments are needed to better define the role of PER in these populations.

Reproductive safety

Reproductive safety is another area where evidence remains limited, and interest in PER during pregnancy is growing given its utility in generalized epilepsies and the need for alternatives to teratogenic agents such as valproate. Available data are derived almost exclusively from observational studies, case series, and pregnancy registry reports involving relatively few exposed pregnancies, with substantial heterogeneity in study design and outcome reporting [45–51].

Current data on PER in pregnancy are derived from approximately 101 reported PER-exposed pregnancies [45–51]. Across these reports, outcomes were broadly similar to those observed with other ASMs, with caesarean delivery

and fetal loss among the most frequently reported events. However, interpretation is limited by small sample sizes, incomplete follow-up, inconsistent outcome definitions, and important confounding factors, including concomitant ASM exposure, maternal epilepsy severity, seizure control during pregnancy, and differences in the timing and duration of PER exposure. Some studies reported relatively high rates of fetal loss, including Maguire (77.8%) [49] and Vázquez *et al*. (38%) [46], but the absence of appropriate comparator groups and the influence of multiple confounders preclude any conclusions regarding causality or drug-specific risk [46–49]. Consequently, the available evidence is insufficient to draw firm conclusions regarding the safety of PER during pregnancy or its effects on fetal and neonatal outcomes. Expansion of prospective pregnancy registries and coordinated international data collection efforts remains a critical research priority to better characterize reproductive safety and inform clinical decision-making.

Future clinical roles

As understanding of AMPA receptor-mediated excitotoxicity evolves, interest has emerged in whether PER may have applications beyond epilepsy in neurological conditions characterized by glutamatergic dysregulation. However, evidence in these areas remains preliminary and should be interpreted cautiously. In a small open-label study of patients undergoing resection for newly diagnosed high-grade glioma, PER produced cortical hyperexcitability levels comparable to levetiracetam, however, there were no clear differences in seizure outcomes or survival and no significant effects on glutamate-related electrophysiologic markers [52]. While these findings suggest biological activity in a disease state associated with altered glutamatergic signaling, the study was not powered to evaluate clinical efficacy and does not support routine use beyond established epilepsy indications.

Similarly, preclinical studies have demonstrated potential neuroprotective effects of PER in experimental ischemic stroke models, where treatment reduced neuronal injury and improved motor outcomes through modulation of neuroinflammatory and ferroptotic pathways [53]. Although these findings provide mechanistic insights and support further investigation, their clinical relevance remains uncertain until validated in human studies.

Patient-centered outcomes

Finally, future research should place greater emphasis on patient-centered outcomes. While seizure reduction remains essential, measures such as quality of life, cognitive and psychiatric well-being, treatment burden, employment, social participation, and caregiver stress are increasingly recognized as equally important indicators of therapeutic success.

Conclusions

The PERMIT Extension study represents an important milestone in the evolution of the PER evidence base. What began as an adjunctive therapy for focal epilepsy has matured into a broad-spectrum ASM with demonstrated effectiveness across diverse seizure types, epilepsy syndromes, and age groups. Sustained long-term retention, consistent real-world effectiveness, and accumulating data in syndromes such as LGS and Dravet syndrome, together with expanding experience in special populations, underscore its growing relevance in contemporary epilepsy care. Behavioral AEs remain the principal tolerability concern and warrant continued vigilance, yet the overall safety profile has remained stable and emerging evidence supports cognitive neutrality. Despite these advances, several critical knowledge gaps persist: robust pregnancy-registry data are needed to clarify maternal and fetal safety; evidence in neonatal seizures and the youngest pediatric populations remains limited; and the absence of prospective head-to-head comparative studies continues to constrain treatment selection. Future work should also prioritize syndrome-specific outcomes and patient-reported measures, including quality of life, treatment burden, and caregiver impact, to better define the contexts in which PER provides the greatest value. As the evidence base continues to expand beyond the boundaries of randomized trials, rigorous investigation across the lifespan will be essential to establishing PER's optimal role within increasingly complex and heterogeneous epilepsy populations.

References

1. Rogawski MA, Hanada T. Preclinical pharmacology of perampanel, a selective non-competitive AMPA receptor antagonist. Acta Neurol Scand Suppl. 2013;(197):19–24.
2. Lattanzi S, Striano P. The impact of perampanel and targeting AMPA transmission on anti-seizure drug discovery. Expert Opin Drug Discov. 2019 Mar;14(3):195–7.
3. French JA, Krauss GL, Biton V, Squillacote D, Yang H, Laurenza A, et al. Adjunctive perampanel for refractory partial-onset seizures: randomized phase III study 304. Neurology. 2012 Aug 7;79(6):589–96.
4. French JA, Krauss GL, Steinhoff BJ, Squillacote D, Yang H, Kumar D, et al. Evaluation of adjunctive perampanel in patients with refractory partial-onset seizures: results of randomized global phase III study 305. Epilepsia. 2013 Jan;54(1):117–25.
5. Krauss GL, Serratosa JM, Villanueva V, Endziniene M, Hong Z, French J, et al. Randomized phase III study 306: adjunctive perampanel for refractory partial-onset seizures. Neurology. 2012 May 1;78(18):1408–15.
6. French JA, Krauss GL, Wechsler RT, Wang XF, DiVentura B, Brandt C, et al. Perampanel for tonic-clonic seizures in idiopathic generalized epilepsy A randomized trial. Neurology. 2015 Sep 15;85(11):950–7.

7. Fogarasi A, Flamini R, Milh M, Phillips S, Yoshitomi S, Patten A, et al. Open-label study to investigate the safety and efficacy of adjunctive perampanel in pediatric patients (4 to <12 years) with inadequately controlled focal seizures or generalized tonic-clonic seizures. Epilepsia. 2020 Jan;61(1):125–37.

8. Villanueva V, D'Souza W, Goji H, Kim DW, Liguori C, McMurray R, et al. PERMIT pooled analysis participants. PERMIT study: a global pooled analysis study of the effectiveness and tolerability of perampanel in routine clinical practice. J Neurol. 2022 Apr;269(4):1957–77.

9. Wechsler RT, Wheless J, Zafar M, Huesmann GR, Lancman M, Segal E, et al. PROVE: Retrospective, non-interventional, Phase IV study of perampanel in real-world clinical care of patients with epilepsy. Epilepsia Open. 2022 Jun;7(2):293–305.

10. Wheless J, Wechsler RT, Penovich P, Segal E, Chez M, Coppola A, et al. Effectiveness, safety and tolerability of perampanel by age group when used to treat people with focal and generalized epilepsy in clinical practice: The PERMIT Extension study. Epilepsy Behav. 2023 Oct;147:109369.

11. Gesche J, Beier CP. Drug resistance in idiopathic generalized epilepsies: Evidence and concepts. Epilepsia. 2022 Dec;63(12):3007–19.

12. Alzahrany M, Punia V. Extreme late onset of genetic generalized epilepsy in older adults and the elderly: A cohort study and literature review. Epilepsia Open. 2023 Mar;8(1):193–99.

13. Vorderwülbecke BJ, Wandschneider B, Weber Y, Holtkamp M. Genetic generalized epilepsies in adults - challenging assumptions and dogmas. Nat Rev Neurol. 2022 Feb;18(2):71–83.

14. Devinsky O, Elder C, Sivathamboo S, Scheffer IE, Koepp MJ. Idiopathic Generalized Epilepsy: Misunderstandings, Challenges, and Opportunities. Neurology. 2024 Feb 13;102(3):e208076.

15. Trinka E, Alsaadi T, Goji H, Maehara T, Takahashi S, Jacobs J, et al. Perampanel for the treatment of people with idiopathic generalized epilepsy in clinical practice. Epilepsia. 2023 Aug;64(8):2094–107.

16. Kwan P, Brodie MJ. Early identification of refractory epilepsy. N Engl J Med. 2000 Feb 3;342(5):314–9.

17. Kwan P, Schachter SC, Brodie MJ. Drug-resistant epilepsy. N Engl J Med. 2011;365:919–26.

18. Brodie MJ, Barry SJ, Bamagous GA, Norrie JD, Kwan P. Patterns of treatment response in newly diagnosed epilepsy. Neurology. 2012 May 15;78(20):1548–54.

19. St Louis EK, Rosenfeld WE, Bramley T. Antiepileptic drug monotherapy: the initial approach in epilepsy management. Curr Neuropharmacol. 2009 Jun;7(2):77–82.

20. Cramer JA, Mintzer S, Wheless J, Mattson RH. Adverse effects of antiepileptic drugs: a brief overview of important issues. Expert Rev Neurother. 2010 Jun;10(6):885–91.

21. Gambardella A, Tinuper P, Acone B, Bonanni P, Coppola G, Perucca E. Selection of antiseizure medications for first add-on use: A consensus paper. Epilepsy Behav. 2021 Sep;122:108087.

22. Thomas SV, Koshy S, Nair CR, Sarma SP. Frequent seizures and polytherapy can impair quality of life in persons with epilepsy. Neurol India. 2005 Mar;53(1):46–50.

23. Alsaadi T, Penovich P, Auvin S, López-Gonzalez J, Gennaro GD, Wheless J, et al. Clinical factors associated with perampanel retention, response, seizure freedom and tolerability: real-world evidence from the PERMIT Extension study. Ther Adv Neurol Disord. 2025 Nov 8;18:17562864251387912.

24. Punia V, Klein P, Mihaylova T, Biton V, Samad O, Ngo LY, et al. Perampanel as monotherapy or first adjunctive therapy in pediatric and adult patients with epilepsy: the first United States-based phase IV open-label ELEVATE study. J Neurol. 2024 Jul;271(7):4587–98.

25. Sun S, Li X, Liu X. Efficacy, tolerability and safety of perampanel in children and adolescents with epilepsy: Systematic review and meta-analysis. Brain Dev. 2023 May;45(5):260–69.

26. Weng Y, Ma B, Lin X. Real-world effectiveness and safety of perampanel for children and adolescents with epilepsy: A meta-analysis with at least 1-year follow-up. Seizure. 2024 Nov;122:96–104.

27. Wang T, Li L, Sun F, Yang Y, Liu X. Efficacy and safety of perampanel for the treatment of epilepsy in adolescents: a meta-analysis. Int J Neurosci. 2023 Dec;133(9):1008–16.

28. Scorrano G, Lattanzi S, Salpietro V, Giannini C, Chiarelli F, Matricardi S. The Cognitive and Behavioural Effects of Perampanel in Children with Neurodevelopmental Disorders: A Systematic Review. J Clin Med. 2024 Jan 10;13(2):372.

29. Datta AN, Xu Q, Sachedina S, Boelman C, Huh L, Connolly MB. Clinical Experience With Perampanel for Refractory Pediatric Epilepsy in One Canadian Center. J Child Neurol. 2017 Aug;32(9):834–9.

30. Fan PF, Zhuo C, Huang M. Efficacy and safety of perampanel for epilepsy: a systematic review and meta-analysis of real-world studies. Eur Rev Med Pharmacol Sci. 2023 Jul;27(13):6027–39.

31. Steinhoff BJ, Staack AM, Hillenbrand BC. Randomized controlled antiepileptic drug trials miss almost all patients with ongoing seizures. Epilepsy Behav. 2017 Jan;66:45–48.

32. Tlusta E, Handoko KB, Majoie M, Egberts TC, Vlcek J, Heerdink ER. Clinical relevance of patients with epilepsy included in clinical trials. Epilepsia. 2008 Aug;49(8):1479–80.

33. Kumar D, Sabet H, Elshahat A, El-Moslemani M, Arafa A, Saleh MGA, et al. Effectiveness and safety of perampanel in Lennox-Gastaut syndrome: a GRADE-assessed systematic review and meta-analysis. Naunyn Schmiedebergs Arch Pharmacol. 2025 Dec;398(12):16521–36.

34. Hasegawa N, Tohyama J. Positive and negative effects of perampanel treatment on psychiatric and behavioral symptoms in adult patients with epilepsy. Epilepsy Behav. 2021 Apr;117:107515.

35. Kanner AM, Patten A, Ettinger AB, Helmstaedter C, Meador KJ, Malhotra M. Does a psychiatric history play a role in the development of psychiatric adverse events to perampanel… and to placebo? Epilepsy Behav. 2021 Dec;125:108380.

36. Brodie MJ, Besag F, Ettinger AB, Mula M, Gobbi G, Comai S, et al. Epilepsy, Antiepileptic Drugs, and Aggression: An Evidence-Based Review. Pharmacol Rev. 2016 Jul;68(3):563–602.

37. Meador KJ, Seliger J, Le S, Li Y, Razavi B, Falco-Walter J, et al. Cognitive and behavioral effects of perampanel 4 mg daily dose. Epilepsy Behav. 2025 Mar;164:110268.

38. Yan C, Liu J, Jiang J, Sun Y, Chen J, Wei K, et al. A non-inferiority randomized controlled study of Perampanel versus Oxcarbazepine monotherapy for post-stroke epilepsy. Seizure. 2025 Feb;125:172–8.

39. Cerulli Irelli E, Roberti R, Borioni MS, Anzellotti F, Belcastro V, Beretta S, et al. Comparative REal-World Evidence (CREW) Study Group. Comparative Effectiveness of Brivaracetam, Cenobamate, Lacosamide, and Perampanel in Focal Epilepsy. JAMA Neurol. 2026 Apr 1;83(4):320–8.

40. Samanta D. Perampanel, Brivaracetam, Cenobamate, Stiripentol, and Ganaxolone in Lennox-Gastaut Syndrome: A Comprehensive Narrative Review. J Clin Med. 2025 Sep 6;14(17):6302.

41. Vossler DG, Porter BE, Kira R, Lee J, Aeby A, Patten A, et al. Efficacy and safety of perampanel in patients with seizures associated with Lennox-Gastaut syndrome: A randomized trial. Epilepsia. 2025 Feb;66(2):379–93.

42. Wang H, Chen H, Ding X, Cao X, Mai J, Zou H, et al. Efficacy and tolerability of perampanel as add-on therapy in Dravet syndrome: A prospective real-world study. Epilepsia Open. 2025 Aug;10(4):1043–53.

43. Alyazidi AS, Muthaffar OY, Bamaga AK, AlAtwi NA, Alshihri SA, Aljezani MA. The Therapeutic Role of Perampanel in Treating Pediatric Patients With Dravet Syndrome: A Scoping Review. Cureus. 2024 Jul 20;16(7):e65017.

44. Miao P, Zhu X, Jin W, Yu L, Li Y, Wang Y, et al. Efficacy of perampanel in pediatric epilepsy with known and presumed genetic etiology. Ann Clin Transl Neurol. 2023 Aug;10(8):1374–82.

45. Goubran J, Okunnu OG, Lavu A, Eltonsy S. Third generation antiseizure medications exposure during pregnancy and neonatal adverse birth outcomes: A systematic review. Sci Prog. 2024 Apr-Jun;107(2):368504241234781.

46. Vazquez B, Tomson T, Dobrinsky C, Schuck E, O'Brien TJ. Perampanel and pregnancy. Epilepsia 2021;62:698–708.

47. Landmark CJ, Rektorli L, Burns ML, Revdal E, Johannessen SI, Brodtkorb E. Pharmacokinetic data on brivaracetam, lacosamide and perampanel during pregnancy and lactation. Epileptic Disord. 2021 Apr 1;23(2):426–31.

48. Alicino AM, Falcicchio G, Boero G, Santarcangelo G, Francavilla T, Trojano M, et al. Perampanel during pregnancy: Description of four cases. Epilepsy Behav Rep. 2021 Oct 8;16:100490.

49. Maguire M. Response to "Perampanel and pregnancy: Could experience be a gloomy lantern that does not even illuminate its bearer?". Epilepsy Behav. 2022 Apr;129:108654.

50. Dmitrenko DV, Schnaider NA, Goroshkin AN, Tomilina AI, Vlasov PN, Sapronova MR. Russian Register of pregnancy and epilepsy. Neurology, Neuropsychiatry, Psychosomatics. 2017 Jun 14;9(1S):21–5.

51. Lee SA, Kim JH. Reply to: "Perampanel and pregnancy: Could experience be a gloomy lantern that does not even illuminate its bearer?". Epilepsy Behav. 2022 Apr;129:108608.

52. Tobochnik S, Regan MS, Dorotan MKC, Reich D, Lapinskas E, Hossain MA, et al. Pilot Trial of Perampanel on Peritumoral Hyperexcitability in Newly Diagnosed High-grade Glioma. Clin Cancer Res. 2024 Dec 2;30(23):5365–73.

53. Lv JM, Pan YJ, Wang X, Zhang MM, Li W, Liu J, et al. Perampanel Regulates Neuroinflammation and Ferroptosis via Activating FSP1 Following Brain Ischemia. J Inflamm Res. 2025 Oct 17;18:14423–37.