Open-label extension study examines whether adjunctive perampanel has long-term effects on cognition in adolescents with partial seizures

SUMMARY OF

Piña-Garza JE, Lagae L, Villanueva V, et al. Long-term effects of adjunctive perampanel on cognition in adolescents with partial seizures. *Epilepsy Behav*. 2018;83:50-58. doi:10.1016/j.yebeh.2018.03.029

INDICATION

FYCOMPA® (perampanel) is indicated in patients with epilepsy aged 4 years and older for partial-onset seizures (POS) with or without secondarily generalized seizures and adjunctive therapy for patients aged 12 years and older for primary generalized tonic-clonic (PGTC) seizures.

SELECTED SAFETY INFORMATION

WARNING: SERIOUS PSYCHIATRIC AND BEHAVIORAL REACTIONS

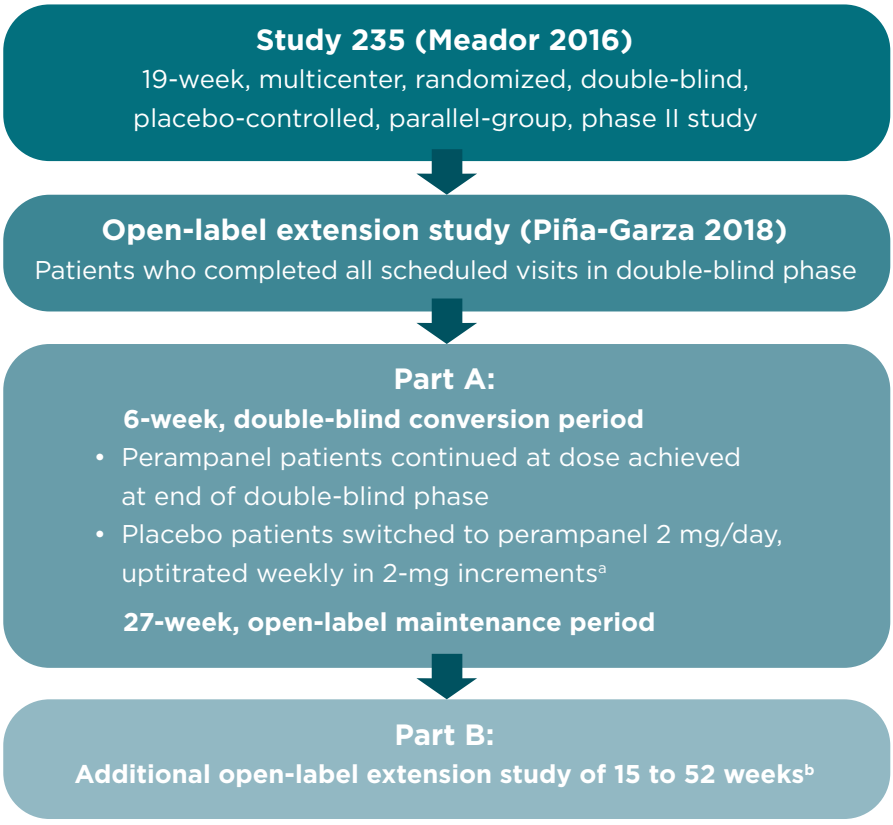
- **Serious or life-threatening psychiatric and behavioral adverse reactions including aggression, hostility, irritability, anger, and homicidal ideation and threats have been reported in patients taking FYCOMPA.**
- **These reactions occurred in patients with and without prior psychiatric history, prior aggressive behavior, or concomitant use of medications associated with hostility and aggression.**
- **Advise patients and caregivers to contact a healthcare provider immediately if any of these reactions or changes in mood, behavior, or personality that are not typical for the patient are observed while taking FYCOMPA or after discontinuing FYCOMPA.**
- **Closely monitor patients particularly during the titration period and at higher doses.**
- **FYCOMPA should be reduced if these symptoms occur and should be discontinued immediately if symptoms are severe or are worsening.**

Please see additional Selected Safety Information throughout and accompanying Prescribing Information, including Boxed WARNING.

Fycompa™ (perampanel) TABLETS 2•4•6•8•10•12 mg ORAL SUSPENSION 0.5 mg/mL CIII

This study evaluated the long-term effects of adjunctive perampanel on cognition, efficacy, safety, and growth and development in adolescents with inadequately controlled partial seizures

Design



[a]All titrations based on tolerance; patients who did not tolerate minimum 2-mg/day dose were discontinued.
[b]For countries without commercially available perampanel or an activated extended-access program.

In the maintenance period of the extension phase, all patients and investigators were unblinded to treatment; patients continued on perampanel up to 12 mg/day. Dose adjustments were permitted during the maintenance period of the extension phase if medically necessary.

Throughout the study, patients continued treatment with 1 to 3 approved antiseizure medication(s) without dose adjustments. For worsening seizures, benzodiazepine administration (maximum once per week) was allowed as rescue medication.

Selected assessments

- **Cognition:** Cognitive Drug Research (CDR) system global cognition T-score
- **Efficacy:** Median percentage reduction in seizure frequency; 50% responder rate
- **Safety:** Treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs)
- **Growth and development:** Weight, height, bone age, Tanner staging (to assess sexual development), and thyroid-stimulating hormone (TSH) and insulin-like growth factor-1 (IGF-1) levels

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SELECTED BASELINE CHARACTERISTICS (N=114)	
Gender	**41.2% female**
Mean age, y (SD)	**14.3 (1.8)**
Seizure type (>2%)[a]	
Simple partial seizure without motor signs	**14.9%**
Simple partial seizure with motor signs	**34.2%**
Complex partial seizures	**71.9%**
Partial seizures with secondary generalization	**49.1%**
Number of concomitant antiseizure medications	
1	**39.5%**
2	**43.0%**
3	**17.5%**
Most frequently used concomitant antiseizure medications (>10%)	
Valproate	**43.0%**
Levetiracetam	**33.3%**
Lamotrigine	**21.9%**
Oxcarbazepine	**20.2%**
Carbamazepine	**18.4%**
Topiramate	**17.5%**
Lacosamide	**10.5%**

[a]Patients could have had more than 1 seizure type.
SD, standard deviation.

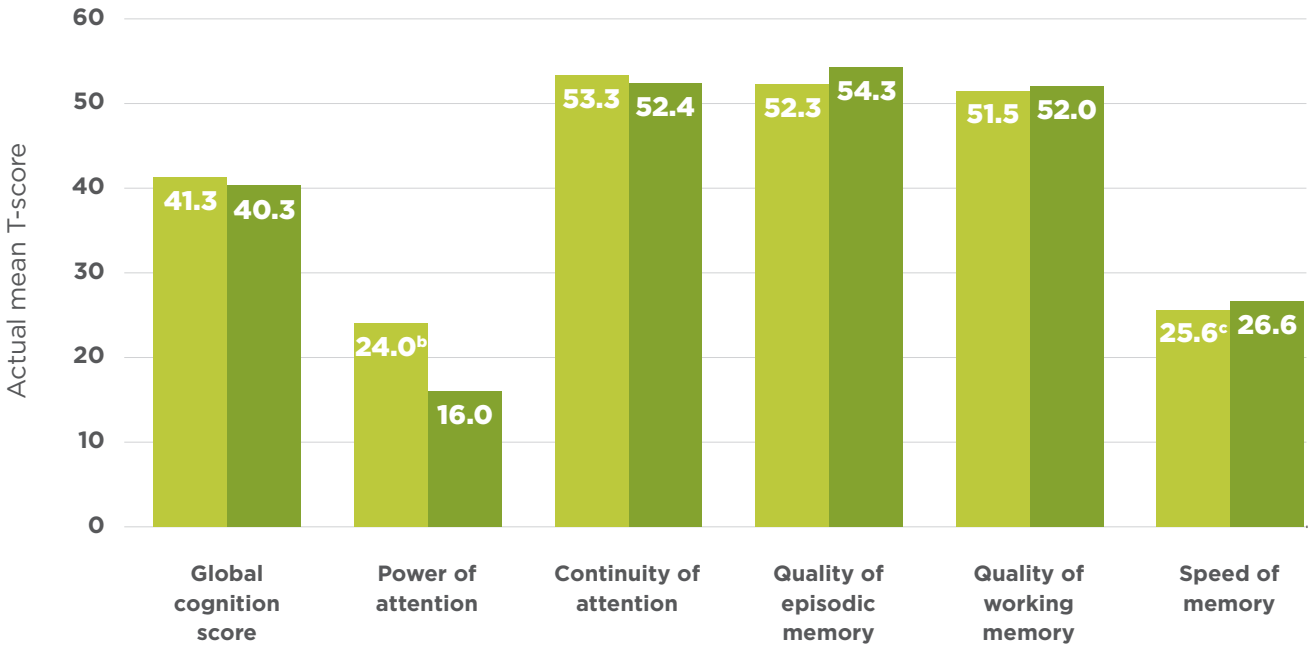
SELECTED SAFETY INFORMATION

SERIOUS PSYCHIATRIC AND BEHAVIORAL REACTIONS

In the partial-onset seizures clinical trials, hostility- and aggression-related adverse reactions occurred in 12% and 20% of patients randomized to receive FYCOMPA at doses of 8 mg and 12 mg per day, respectively, compared to 6% of patients in the placebo group. These effects were dose-related and generally appeared within the first 6 weeks of treatment, although new events continued to be observed through more than 37 weeks. These effects in FYCOMPA-treated patients led to dose reduction, interruption, and discontinuation more frequently than placebo-treated patients. Homicidal ideation and/or threat have also been reported postmarketing in patients treated with FYCOMPA. The combination of alcohol and FYCOMPA significantly worsened mood and increased anger. Patients taking FYCOMPA should avoid the use of alcohol. Patients, their caregivers, and families should be informed that FYCOMPA may increase the risk of psychiatric events. Patients should be monitored during treatment and for at least one month after the last dose of FYCOMPA, and especially when taking higher doses and during the initial few weeks of drug therapy (titration period) or at other times of dose increases. Similar serious psychiatric and behavioral events were observed in the primary generalized tonic-clonic (PGTC) seizure clinical trial.

Long-term effects of FYCOMPA on several measures of cognition in adolescents with partial seizures

CDR system global cognition T-score and 5 core domain T-scores[a]



[a]Full analysis set for cognition; N=112. All cognitive measure scores were expressed as T-scores. T-scores are normalized standard scores and have a mean of 50 and an SD of 10. The T-scores are based on the norms from healthy age-matched controls from the CDR system database. A paired t-test was used to assess the statistical significance of changes in the CDR system global score and core domain T-scores. Analyses for individual domains of the CDR were not corrected for multiplicity.
[b]For power of attention, it should be noted that patients had Baseline impairments of over two SDs on this measure of focused attention and information processing compared with healthy age-matched controls.
[c]For speed of memory, it should be noted that patients had a large Baseline impairment in their ability to rapidly retrieve information held in either their working or episodic memory.

SELECTED SAFETY INFORMATION

SUICIDAL BEHAVIOR AND IDEATION

Antiepileptic drugs (AEDs), including FYCOMPA, increase the risk of suicidal thoughts or behavior in patients. Anyone considering prescribing FYCOMPA or any other AED must balance the risk of suicidal thoughts or behavior with the risk of untreated illness. Epilepsy and many other illnesses for which AEDs are prescribed are themselves associated with morbidity and mortality and an increased risk of suicidal thoughts and behavior. Patients, their caregivers, and families should be informed of the risk and advised to monitor and immediately report the emergence or worsening of depression, suicidal thoughts or behavior, thoughts about self-harm and/or any unusual changes in mood or behavior. Should suicidal thoughts and behavior emerge during treatment, consider whether the emergence of these symptoms in any given patient may be related to the illness being treated.

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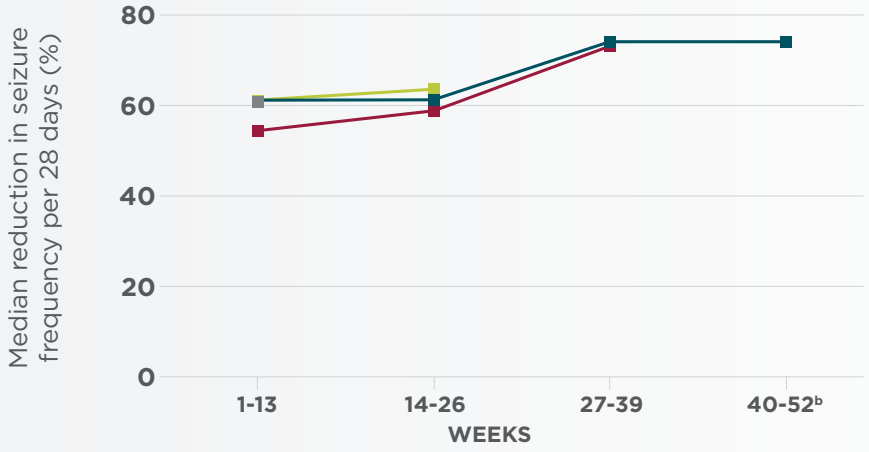
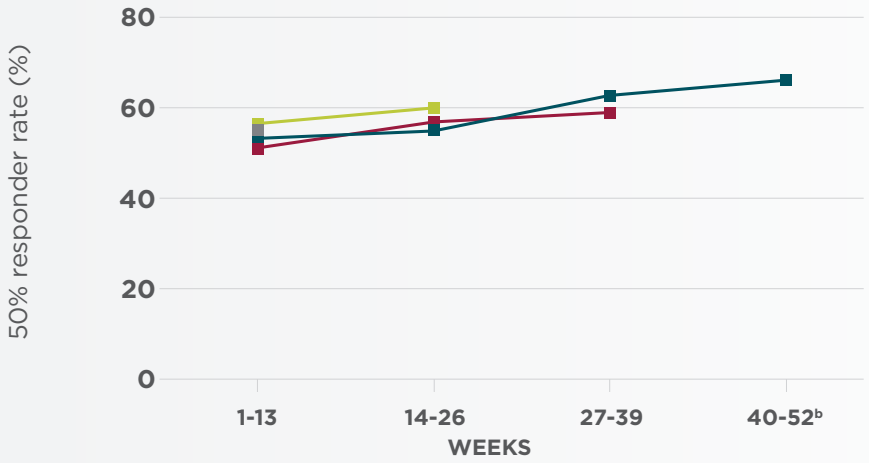
Seizure outcomes were consistent with those observed in the double-blind phase of the study[a]

Median percentage reduction in seizure frequency per 28 days



50% responder rate



PERAMPANEL DURATION:

- ≥13 WEEKS (n=109)
- ≥26 WEEKS (n=107)
- ≥39 WEEKS (n=90)
- ≥52 WEEKS (n=67)

[a]Full analysis set for efficacy (N=114).
[b]N=53.

SELECTED SAFETY INFORMATION

DIZZINESS AND GAIT DISTURBANCE

FYCOMPA caused dose-related increases in events related to dizziness and disturbance in gait or coordination. Dizziness and vertigo were reported in 35% and 47% of patients in the partial-onset seizure trials randomized to receive FYCOMPA at doses of 8 mg and 12 mg per day, respectively, compared to 10% of placebo-treated patients. Gait disturbance related events were reported in 12% and 16% of patients in the partial-onset seizure clinical trials randomized to receive FYCOMPA at doses of 8 mg and 12 mg per day, respectively, compared to 2% of placebo-treated patients. These adverse reactions occurred mostly during the titration phase. These adverse reactions were also observed in the PGTC seizure clinical trial.

The safety profile of perampanel was consistent with that observed in prior clinical studies

Safety

- Most common TEAEs included dizziness (29.8%, n=34) and somnolence (19.3%, n=22)
  - Most common TEAEs related to hostility/aggression were aggression (11.4%, n=13) and irritability (6.1%, n=7)
- Majority of most common TEAEs occurred early in treatment
  - Among patients who received perampanel for ≥52 weeks, the incidence of the most common adverse events was 74.6% at Weeks 1 to 13 and 26.9% at Weeks 40 to 52
- TEAEs resulted in treatment discontinuation in 7 patients (6.1%)
- 23 SAEs occurred in 19 patients; only 2 occurred in >1 patient: Convulsion (n=4) and aggression (n=4)

STUDY LIMITATIONS

- Open label
- Small number of patients
- Lack of placebo or active control group

SELECTED SAFETY INFORMATION

SOMNOLENCE AND FATIGUE

FYCOMPA caused dose-dependent increases in somnolence and fatigue-related events. Somnolence was reported in 16% and 18% of patients in the partial-onset seizure trials randomized to receive FYCOMPA at doses of 8 mg and 12 mg per day, respectively, compared to 7% of placebo-treated patients. Fatigue-related events were reported in 12% and 15% of patients in the partial-onset seizure trials randomized to receive FYCOMPA at doses of 8 mg and 12 mg per day, respectively, compared to 5% of placebo-treated patients. These adverse reactions occurred mostly during the titration phase. These adverse reactions were also observed in the PGTC seizure clinical trial. Patients should be advised against engaging in hazardous activities requiring mental alertness, such as operating motor vehicles or dangerous machinery, until the effect of FYCOMPA is known. Patients should be carefully observed for signs of central nervous system (CNS) depression when FYCOMPA is used with other drugs with sedative properties because of potential additive effects.

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SELECTED SAFETY INFORMATION

FALLS

Falls were reported in 5% and 10% of patients in the partial-onset seizure clinical trials randomized to receive FYCOMPA at doses of 8 mg and 12 mg per day, respectively, compared to 3% of placebo-treated patients.

DRUG REACTION WITH EOSINOPHILIA AND SYSTEMIC SYMPTOMS (DRESS)

DRESS, also known as **multiorgan hypersensitivity**, has been reported in patients taking AEDs, including FYCOMPA. DRESS may be fatal or life-threatening. DRESS typically, although not exclusively, presents with fever, rash, lymphadenopathy, and/or facial swelling, in association with other organ system involvement. If signs or symptoms are present, immediately evaluate the patient and discontinue FYCOMPA if an alternative etiology for signs or symptoms cannot be established.

WITHDRAWAL OF AEDs

A gradual withdrawal is generally recommended with AEDs to minimize the potential of increased seizure frequency, but if withdrawal is a response to adverse events, prompt withdrawal can be considered.

MOST COMMON ADVERSE REACTIONS

The most common adverse reactions in patients aged 12 years and older receiving FYCOMPA (≥5% and ≥1% higher than placebo) include dizziness, somnolence, fatigue, irritability, falls, nausea, weight gain, vertigo, ataxia, headache, vomiting, contusion, abdominal pain, and anxiety. Adverse reactions in patients 4 to <12 years were generally similar to patients aged 12 years and older.

DRUG INTERACTIONS

FYCOMPA may decrease the efficacy of contraceptives containing levonorgestrel. Plasma levels of perampanel were decreased when administered with known moderate and strong CYP3A4 inducers, including, carbamazepine, phenytoin, or oxcarbazepine. Multiple dosing of FYCOMPA 12 mg per day enhanced the effects of alcohol on vigilance and alertness, and increased levels of anger, confusion, and depression. These effects may also be seen when FYCOMPA is used in combination with other CNS depressants.

PREGNANCY AND LACTATION

Physicians are advised to recommend that pregnant patients taking FYCOMPA enroll in the North American Antiepileptic Drug (NAAED) Pregnancy Registry. Caution should be exercised when FYCOMPA is administered to pregnant or nursing women as there are no adequate data on the developmental risk associated with use in pregnant women, and no data on the presence of perampanel in human milk, the effects on the breastfed child, or the effects of the drug on milk production.

HEPATIC AND RENAL IMPAIRMENT

Use in patients with severe hepatic or severe renal impairment is not recommended. Dosage adjustments are recommended in patients with mild or moderate hepatic impairment. Use with caution in patients with moderate renal impairment.

DRUG ABUSE AND DEPENDENCE

FYCOMPA is a Schedule III controlled substance and has the potential to be abused and lead to drug dependence and withdrawal symptoms including anxiety, nervousness, irritability, fatigue, asthenia, mood swings, and insomnia.

REFERENCES

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Long-term effects of adjunctive perampanel on cognition in adolescents with partial seizures

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ABSTRACT

Objective: The aim of this study was to evaluate long-term effects of adjunctive perampanel on cognition, efficacy, growth, safety, and tolerability in adolescents with inadequately controlled partial seizures.
Methods: Study 235, a multicenter, randomized, double-blind, placebo-controlled, parallel-group, Phase II study with an open-label extension phase (NCT01161524), was primarily designed to assess the effects of adjunctive perampanel on cognition. Patients (aged ≥12 to <18 years) had a diagnosis of epilepsy with inadequately controlled partial seizures, with or without secondary generalization, despite receiving 1–3 antiepileptic drugs. During the double-blind phase, adjunctive perampanel or placebo was administered over a 6-week titration period and a 13-week maintenance period up to 12 mg/day. During the extension phase, all patients received perampanel. Data from the extension phase are presented here. Study endpoints included change from baseline in Cognitive Drug Research (CDR) measures of cognition, seizure frequency, growth, development, the occurrence of treatment-emergent adverse events (TEAEs), and laboratory values.
Results: A total of 114 patients entered the extension phase (prior double-blind treatment: placebo, n = 41; perampanel, n = 73). Perampanel had no effect on the CDR system global cognition score, continuity of attention, quality of episodic memory, quality of working memory, or speed of memory but was associated with a significant decline in power of attention at end of treatment compared with baseline ($p = 0.03$). There were no effects on language skills or manual dexterity from baseline to end of treatment. At Weeks 40–52, median reduction in seizure frequency was 74.1%, and 50% responder rate was 66.0%. There were no clinically relevant effects of perampanel on growth or development at end of treatment compared with baseline. Overall, 84.2% of patients experienced at least one TEAE and 70.2% experienced at least one treatment-related TEAE. The most common TEAEs were dizziness (29.8%) and somnolence (19.3%). The TEAEs resulted in the discontinuation of treatment in 6.1% of patients.
Conclusions: In keeping with the 19-week double-blind phase, long-term adjunctive treatment with perampanel did not have any significant overall effects on the CDR system global cognition score in adolescent patients with inadequately controlled partial seizures. Similar trends were observed across the individual CDR system domains. Adjunctive perampanel showed sustained long-term seizure control and had a safety and tolerability profile similar to that observed in prior clinical studies.

Abbreviations: AED, antiepileptic drug; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; CDR, Cognitive Drug Research; COWAT, Controlled Oral Word Association; EIAED, enzyme-inducing antiepileptic drug; IGF-1, insulin-like growth factor-1; LGPT, Lafayette Grooved Pegboard Test; SAE, serious adverse event; SD, standard deviation; TEAE, treatment-emergent adverse event; TSH, thyroid-stimulating hormone.

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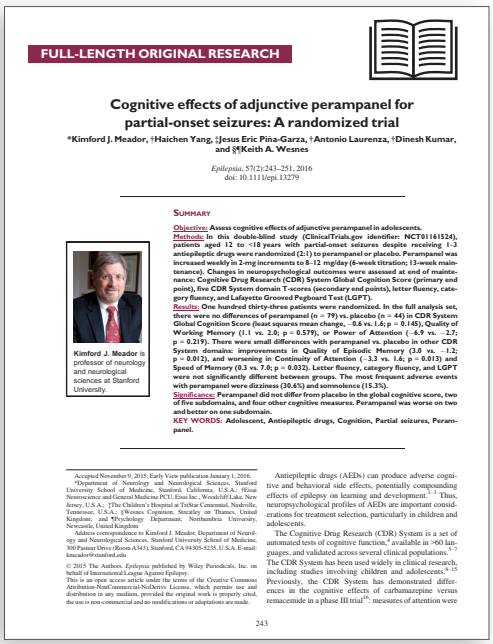

FULL-LENGTH ORIGINAL RESEARCH

Cognitive effects of adjunctive perampanel for partial-onset seizures: A randomized trial

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Epilepsia, 57(2):243–251, 2016
doi: 10.1111/epi.13279

SUMMARY

Objective: Assess cognitive effects of adjunctive perampanel in adolescents.
Methods: In this double-blind study (ClinicalTrials.gov identifier: NCT01161524), patients aged 12 to <18 years with partial-onset seizures despite receiving 1–3 antiepileptic drugs were randomized (2:1) to perampanel or placebo. Perampanel was increased weekly in 2-mg increments to 8–12 mg/day (6-week titration; 13-week maintenance). Changes in neuropsychological outcomes were assessed at end of maintenance: Cognitive Drug Research (CDR) System Global Cognition Score (primary end point), five CDR System domain T-scores (secondary end points), letter fluency, category fluency, and Lafayette Grooved Pegboard Test (LGPT).
Results: One hundred thirty-three patients were randomized. In the full analysis set, there were no differences of perampanel (n = 79) vs. placebo (n = 44) in CDR System Global Cognition Score (least squares mean change, −0.6 vs. 1.6; p = 0.145), Quality of Working Memory (1.1 vs. 2.0; p = 0.379), or Power of Attention (−6.9 vs. −2.7; p = 0.219). There were small differences with perampanel vs. placebo in other CDR System domains: improvements in Quality of Episodic Memory (3.0 vs. −1.2; p = 0.012), and worsening in Continuity of Attention (−3.3 vs. 1.6; p = 0.013) and Speed of Memory (0.3 vs. 7.0; p = 0.032). Letter fluency, category fluency, and LGPT were not significantly different between groups. The most frequent adverse events with perampanel were dizziness (30.6%) and somnolence (15.3%).
Significance: Perampanel did not differ from placebo in the global cognitive score, two of five subdomains, and four other cognitive measures. Perampanel was worse on two and better on one subdomain.
KEY WORDS: Adolescent, Antiepileptic drugs, Cognition, Partial seizures, Perampanel.

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Antiepileptic drugs (AEDs) can produce adverse cognitive and behavioral side effects, potentially compounding effects of epilepsy on learning and development.[1–3] Thus, neuropsychological profiles of AEDs are important considerations for treatment selection, particularly in children and adolescents.

The Cognitive Drug Research (CDR) System is a set of automated tests of cognitive function,[4] available in >60 languages, and validated across several clinical populations.[5–7] The CDR System has been used widely in clinical research, including studies involving children and adolescents.[8–13] Previously, the CDR System has demonstrated differences in the cognitive effects of carbamazepine versus remacemide in a phase III trial[14]; measures of attention were

Meador KJ, Yang H, Piña-Garza JE, et al. Cognitive effects of adjunctive perampanel for partial-onset seizures: A randomized trial. *Epilepsia*. 2016;57(2):243-251. doi:10.1111/epi.13279