# Practice guideline update summary: Efficacy and tolerability of the new antiepileptic drugs II: Treatment-resistant epilepsy

Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology and the American Epilepsy Society

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## Abstract

### Objective
To update the 2004 American Academy of Neurology guideline for managing treatment-resistant (TR) epilepsy with second- and third-generation antiepileptic drugs (AEDs).

### Methods
2004 criteria were used to systemically review literature (January 2003 to November 2015), classify pertinent studies according to the therapeutic rating scheme, and link recommendations to evidence strength.

### Results
Forty-two articles were included.

### Recommendations
The following are established as effective to reduce seizure frequency (Level A): immediate-release pregabalin and perampanel for TR adult focal epilepsy (TRAFE); vigabatrin for TRAFE (not first-line treatment); rufinamide for Lennox-Gastaut syndrome (LGS) (add-on therapy). The following should be considered to decrease seizure frequency (Level B): lacosamide, eslicarbazepine, and extended-release topiramate for TRAFE (ezogabine production discontinued); immediate- and extended-release lamotrigine for generalized epilepsy with TR generalized tonic-clonic (GTC) seizures in adults; levetiracetam (add-on therapy) for TR childhood focal epilepsy (TRCFE) (1 month–16 years), TR GTC seizures, and TR juvenile myoclonic epilepsy; clobazam for LGS (add-on therapy); zonisamide for TRCFE (6–17 years); oxcarbazepine for TRCFE (1 month–4 years). The text presents Level C recommendations. AED selection depends on seizure/syndrome type, patient age, concomitant medications, and AED tolerability, safety, and efficacy. This evidence-based assessment informs AED prescription guidelines for TR epilepsy and indicates seizure types and syndromes needing more evidence. A recent Food and Drug Administration (FDA) strategy allows extrapolation of efficacy across populations; therefore, for focal epilepsy, eslicarbazepine and lacosamide (oral only for pediatric use) as add-on or monotherapy in persons ≥4 years of age and perampanel as monotherapy received FDA approval.

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# Glossary

**AAN** = American Academy of Neurology; **AE** = adverse event; **AED** = antiepileptic drug; **AES** = American Epilepsy Society; **CLB** = clobazam; **ESL** = eslicarbazepine; **EZG** = ezogabine; **FBM** = felbamate; **FDA** = Food and Drug Administration; **GBP** = gabapentin; **GE** = generalized epilepsy; **GTC** = generalized tonic-clonic; **JME** = juvenile myoclonic epilepsy; **LCM** = lacosamide; **LEV** = levetiracetam; **LEV-XR** = extended-release levetiracetam; **LTG** = lamotrigine; **LTG-XR** = extended-release lamotrigine; **OXC** = oxcarbazepine; **OXC-XR** = extended-release oxcarbazepine; **PER** = perampanel; **PGB** = pregabalin; **PGB-CR** = controlled-release pregabalin; **PGB-IR** = immediate-release pregabalin; **RFN** = rufinamide; **TGB** = tiagabine; **TPM** = topiramate; **TPM-XR** = extended-release topiramate; **TR** = treatment-resistant; **TRAFE** = treatment-resistant adult focal epilepsy; **VGB** = vigabatrin; **ZNS** = zonisamide.

In 2004, the American Academy of Neurology (AAN) and the American Epilepsy Society (AES) published a guideline on felbamate (FBM)[1] and another guideline on 8 second-generation antiepileptic drugs (AEDs) (table 1 shows principal findings).[2] Since the 2004 publications, the US Food and Drug Administration (FDA) approved 6 new third-generation AEDs and 2 older AEDs (table 2). This update reviews new evidence for efficacy of these AEDs in managing treatment-resistant (TR) focal epilepsies and generalized epilepsies (GEs) in children and adults. The FDA also approved an additional new drug, brivaracetam, and an additional indication for perampanel (for primary generalized tonic-clonic [GTC] seizures) since the 2004 guideline that are not included in this update. These were excluded because they received FDA approval after the date of the last literature search update in November 2015; per the AAN guideline development process, studies not retrieved in a literature search cannot be included in the systematic review.

A companion guideline update examines the evidence in new-onset focal epilepsy or GE.

This article summarizes the guideline findings, conclusions, and recommendations. The complete guideline, including appendices e-1 through e-6, cited here, is available at links.lww.com/WNL/A563, and tables e-1 through e-6 at links.lww.com/WNL/A561.

# Description of the analytic process

The AAN and AES convened an expert panel to develop this guideline using the 2004 AAN guideline development process.[3] The complete guideline (data supplement at links.lww.com/WNL/A563) describes the literature search strategy and evidence review process. Class IV studies are not discussed.

⊕ **Supplemental Data**

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# Analysis of evidence

## For adult patients with TR focal epilepsy, are these AEDs effective as adjunctive therapy in reducing seizure frequency?

### Pregabalin

Pregabalin (PGB) was examined in 2 Class I and 2 Class II studies on immediate-release PGB (PGB-IR)[4–7] and 1 Class I study of controlled-release PGB (PGB-CR).[8]

PGB was significantly superior to placebo at daily doses of 150, 300, and 600 mg, with >50% responder rates and greater median percent seizure reduction, in a dose-related manner. Dizziness and sedation were the most frequently occurring adverse events (AEs) and AE-related drug discontinuation reported, which increased in frequency with higher doses.

A Class I study compared placebo with PGB-CR 165 and 330 mg/d.[e5] The 3 arms failed to differ. AEs and AE-related discontinuation rates were higher in the high-dose arm and similar to the trials with PGB-IR.[6–8]

*Conclusions*

PGB-IR is effective as add-on therapy for TR adult focal epilepsy (TRAFE) (2 Class I studies). Efficacy and AEs increased with higher doses. PGB-CR is probably not effective (1 Class I study).

*Clinical context*

The initial PGB-IR doses were higher than typically used in clinical practice (25–50 mg/d) and may have led to higher AE occurrence rate. The lack of efficacy of PGB-CR compared with placebo may be due to an exceptionally high placebo responder rate or the failure to use maximal doses (e.g., 600 mg/d).

### Lacosamide

Lacosamide (LCM) and placebo were compared in 1 Class I and 2 Class II studies.[9–11] LCM at doses of 400 and 600 mg/d showed significantly higher responder rates and greater median reduction of seizures than placebo. One Class II study[10] showed 600 mg/d yielded a greater reduction in secondarily GTC seizures. Dose-dependent discontinuation

**Table 1** Summary of first guidelines on the use of antiepileptic drugs (AEDs) in treatment-resistant epilepsy, based on Level A and B recommendations[3]

| AED | Adjunctive focal adult | Focal monotherapy | IGE | LGS | Adjunctive focal pediatric |
|---|---|---|---|---|---|
| Gabapentin | Yes | No | No | No | Yes |
| Lamotrigine | Yes | Yes | Yes (only in CAE) | Yes | Yes |
| Levetiracetam | Yes | No | No | No | No |
| Oxcarbazepine | Yes | Yes | No | No | Yes |
| Tiagabine | Yes | No | No | No | No |
| Topiramate | Yes | Yes | Yes | Yes | Yes |
| Zonisamide | Yes | No | No | No | No |

Abbreviations: CAE = childhood absence epilepsy; IGE = idiopathic generalized epilepsy; LGS = Lennox-Gastaut syndrome.

because of AEs was not universally observed. AEs were diplopia, vertigo, and emesis in the Class I study[9] and dizziness, nausea, fatigue, ataxia, diplopia, and nystagmus in the Class II studies.[10,11]

A Class III study assessed the parenteral formulation of LCM.[12] Headache, dizziness, and somnolence were the most common AEs, with increased frequency for doses >400 mg/d.

*Conclusion*
LCM is probably effective in TRAFE (1 Class I study).

*Clinical context*
Initial LCM doses were higher than typically used in clinical practice (50–100 mg/d) and may have led to a higher AE occurrence rate. Pooled data suggested dizziness was twice as frequent when LCM was used with other sodium channel drugs.[13]

**Table 2** Mechanism of action of the 8 newly approved antiepileptic drugs (AEDs)

| AED | Mechanism of action |
|---|---|
| Clobazam | Binding to benzodiazepine at the GABA$_A$ ligand–gated chloride channel complex |
| Eslicarbazepine | Use-dependent blockage of voltage-sensitive sodium channels |
| Ezogabine | Positive allosteric modulator of KCNQ2-5; positive allosteric modulator of GABA$_A$ receptors |
| Lacosamide | Slow inactivation of voltage-gated sodium channels; binds to CRMP-2 |
| Perampanel | AMPA receptor antagonist |
| Pregabalin | Binding to the α2-δ protein subunit of voltage-gated calcium channels |
| Rufinamide | Use-dependent blockage of voltage-sensitive sodium channels |
| Vigabatrin | Inactivation of GABA transaminase |

**Rufinamide**
Rufinamide (RFN) and placebo were compared in 3 Class I studies.[14–16] RFN was superior to placebo in reduction of median seizure frequency per 28 days and in >50% responder rates; 400 mg/d was the lowest effective dose. Effects were consistently modest.

The most frequent AEs were dizziness, fatigue, nausea, somnolence, diplopia, confusion, ataxia, and impaired concentration.

*Conclusion*
RFN is effective as add-on therapy for LGS, but benefits are modest (3 Class I studies).

**Ezogabine**
Ezogabine (EZG) and placebo were compared in 3 Class II studies.[17–19] EZG at 600, 900, or 1,200 mg/d was superior to placebo for median percent seizure reduction and responder rates.

Treatment-related AEs were dose-dependent and included dizziness, somnolence, headache, and fatigue. The most common AEs resulting in discontinuation were dizziness and somnolence. In a Class III study,[20] a significantly higher AE rate occurred with titration rates of <7 days.

*Conclusions*
EZG is probably effective as add-on therapy for TRAFE (3 Class II studies).

*Clinical context*
In April 2013, the FDA issued a warning that EZG can cause blue skin discoloration and retina pigment changes, and recommended that any patient taking EZG have baseline and periodic eye examinations. Ezogabine production was discontinued in June 2017.

**Vigabatrin**
Vigabatrin (VGB) and placebo were assessed in 2 Class I studies.[21,22] VGB doses at 1, 3, and 6 g/d yielded significantly

higher responder rates and median reduction in monthly seizure frequency. Fatigue and drowsiness were the most frequent AEs, with a higher drug discontinuation rate in the 6 mg/d group.

In 1997, 1 study found irreversible retinopathies resulting in bilateral concentric constriction of visual fields associated with higher cumulative doses and increasing age.[23] The FDA requires patients to undergo visual field examinations every 3 months.

*Conclusion*
VGB is effective as add-on therapy in TRAFE (2 Class I studies).

*Clinical context*
Benefits of VGB should be weighed against the risks, particularly risk of irreversible retinopathy.

**Clobazam**
Clobazam (CLB) and placebo were assessed in 3 Class III studies, 2 of which had <30 participants, and the larger study included both focal epilepsy and GE.[24–26] Doses in the larger trial ranged from 10–40 mg/d.[24] Patients randomized to CLB had significantly greater seizure frequency reduction and responder rates. AEs were more frequent with CLB and included sedation, dizziness, irritability, depression, and disinhibition.

*Conclusion*
CLB is possibly effective as add-on therapy for TRAFE (3 Class III studies). Generalizability may be limited (2 studies had small numbers; the larger study had possibly mixed groups of focal and generalized epilepsy types).

**Perampanel**
Perampanel (PER) was compared with placebo in 3 Class I studies.[27–29] Doses of 4, 8, and 12 mg/d were superior to placebo in median percent reduction in seizure frequency per 28 days. The dose response rate varied between the studies, perhaps because of a very high placebo rate.

The most common AEs included dizziness, ataxia, falls, headache, somnolence, fatigue, irritability, depression, nausea, and weight gain. AEs were dose-related and occurred during both titration and maintenance phases. Irritability and aggressive behavior prompted a package insert warning.

*Conclusion*
PER is established as effective as add-on therapy in TRAFE (3 Class I studies).

*Clinical context*
Patients should be monitored closely for the occurrence of psychiatric AEs, in particular irritability and aggressive behavior.

**Eslicarbazepine**
Eslicarbazepine (ESL) and placebo were compared in 3 studies (1 Class I, 1 Class II, 1 Class III).[30–32] Single daily doses of 400, 800, and 1,200 mg were investigated. ESL at 800 mg/d and 1,200 mg/d significantly reduced seizure frequency per 4-week period in all 3 studies and yielded significantly higher responder rates in the Class I and III studies. In the Class I study, the seizure-free rate was higher for the 1,200 mg dose.

Treatment-related AEs were generally dose-dependent, including those leading to drug discontinuation. The most frequent AEs were dizziness, headache, diplopia, somnolence, nausea, emesis, and coordination difficulties.

*Conclusion*
ESL doses of 800 and 1,200 mg/d are probably effective in TRAFE (1 Class I study).

*Clinical context*
The Class I study may have limited generalizability because 100% of patients were Caucasian. Tolerability may have been affected, as >50% of patients were concurrently taking carbamazepine, which is chemically related to ESL.

**Extended-release oxcarbazepine**
One Class II study compared the extended-release formulation of oxcarbazepine (OXC-XR) with placebo.[33] Significant differences between OXC-XR and placebo were achieved with the 2,400 mg/d dose for responder rates and median percent seizure rate reduction. Placebo rates outside the United States were very high. When only the North American cohort was assessed, the 1,200 mg/d dose was superior to placebo. The most frequent AEs, including those leading to drug discontinuation, were dizziness, ataxic gait, nausea, vomiting, headache, somnolence, fatigue, and diplopia.

*Conclusion*
OXC-XR 2,400 mg/d is possibly effective for treating TRAFE (1 Class II study).

**Extended-release topiramate**
A Class I study investigated the extended-release formulation of topiramate (TPM-XR) at 200 mg/d.[34] It was superior to placebo for responder rates and median percent reduction in weekly focal seizure rates. Discontinuation because of AEs was more frequent in patients randomized to TPM-XR; the most frequent AEs were somnolence, paresthesia, and weight loss.

*Conclusion*
TPM-XR is probably effective as add-on therapy for TRAFE (1 Class I study).

**Recommendations**
For TRAFE, immediate-release PGB and PER are established as effective to reduce seizure frequency (Level A). LCM, ESL, and TPM-XR use should also be considered to decrease seizure frequency in this population (Level B). VGB and RFN

should be considered established as effective for decreasing seizure frequency in TRAFE (Level A) but are not first-line agents (retinopathy risk with VGB and modest benefit with RFN). EZG use should be considered to decrease seizure frequency in this population (Level B) but carries a serious risk of skin and retinal discoloration. CLB and OXC-XR use may be considered to decrease seizure frequency in TRAFE (Level C).

### For adult patients with TR focal epilepsy, are these AEDs effective in reducing seizure frequency when used as monotherapy?

In the 2004 guideline, lamotrigine (LTG), oxcarbazepine (OXC), and topiramate (TPM) were found to be effective in TRAFE. Since then, 5 Class III conversion-to-monotherapy studies have been conducted using historical controls. One study evaluated extended-release levetiracetam (LEV-XR),[35] 1 evaluated PGB,[36] 1 evaluated LCM,[37] and 2 evaluated ESL.[38,39]

In the LEV-XR study, 1,000 and 2,000 mg/d doses were used.[35] In the PGB study, 150 and 600 mg/d doses were evaluated.[36] For LCM, 300 and 400 mg/d doses were compared with historical controls.[37] The ESL studies investigated 1,200 and 1,600 mg/d doses.[38,39]

In all 4 drugs, the predicted exit rate was significantly lower for patients randomized to the higher doses for LEV-XR and PGB and to both doses for LCM and ESL compared with the historical controls. The most frequent AEs associated with LEV-XR included somnolence, headaches, and convulsions and did not differ between the 2 doses. For PGB, the most frequent AEs were similar to those reported in the add-on PGB trials previously described.[6–8] For LCM, the most common AEs were dizziness, headache, nausea, convulsions, somnolence, and fatigue, most of which were of mild to moderate severity and comparable between the 2 doses; dizziness occurred more in the 400-mg group. For ESL, the most frequent AEs included dizziness, headache, fatigue, somnolence, nausea, and nasopharyngitis and were dose-dependent.

### Conclusions

ESL is possibly effective as monotherapy for TRAFE (2 Class III studies). Evidence is insufficient to determine the efficacy of LCM, LEV-XR, or PGB as monotherapy for TRAFE (1 Class III study per drug). No new Class I, II, or III studies have been published on CLB, EZG, gabapentin (GBP), PER, RFN, tiagabine (TGB), VGB, or zonisamide (ZNS).

### Recommendations

ESL use may be considered to decrease seizure frequency as monotherapy for TRAFE (Level C).

Data are insufficient to recommend the use of second- and the other third-generation AEDs as monotherapy in TRAFE (Level U).

### For adult and pediatric patients with TR GE, are these AEDs effective in reducing seizure frequency when used as adjunctive therapy (compared with no adjunctive therapy)?

The 2004 guidelines found only TPM to be effective as add-on therapy in TR GTC seizures in adults and children. Since then, 3 LTG[40,e1,e2] and 2 levetiracetam (LEV)[e3,e4] (links.lww.com/WNL/A562) studies have been published.

### Lamotrigine

LTG to treat TR GTC at several doses (depending on age and type of additional AED used) were compared with placebo in 1 Class II study with patients aged 2–55 years.[40] Twelve-week median percent reduction of GTC seizure frequency and responder rates were significantly higher for patients randomized to LTG. The most common LTG-related AEs included dizziness, somnolence, and nausea.

A second Class II study[e1] demonstrated significant differences in median percent decrease from baseline in GTC seizures favoring LTG during both escalation and maintenance periods. AEs leading to drug discontinuation were rare. No rashes were reported.

Similar findings were obtained in a Class I study that included adolescents and adults using extended-release LTG (LTG-XR).[e2] Those on LTG-XR experienced a significantly greater median percent reduction in weekly GTC seizure frequency and had a higher responder rate. Nausea, vomiting, and diplopia were the most frequent AEs related to LTG-XR.

*Conclusion*

Both LTG-XR and immediate-release LTG are probably effective as add-on therapy for TR GTC seizures (1 Class I study for LTG-XR; 2 Class II studies for immediate-release LTG).

### Levetiracetam

Two Class I studies compared 3,000 mg/d LEV and placebo in TR GE. One study included patients aged 4–65 years.[e3] LEV demonstrated significantly greater responder rates and GTC-free frequency. The second study assessed adolescents and adults with juvenile myoclonic epilepsy (JME) or juvenile absence epilepsy.[e4] Compared with those on placebo, significantly more patients on LEV had a >50% reduction in the number of days per week with myoclonic seizures, became free of myoclonic seizures, and became free of all seizure types. In the first study, more patients on placebo discontinued therapy because of AEs, but irritability, fatigue, somnolence, and headache occurred in patients on LEV. Somnolence and neck pain were the only 2 AEs seen with greater frequency among patients on LEV in the second study.

*Conclusions*

LEV is probably effective as add-on therapy for TR GE presenting with GTC seizures (1 Class I study). LEV is probably effective as add-on therapy for TR JME and juvenile absence

seizures (1 Class I study). The data from these studies could be generalized to all patients with TR GE; however, the requirement of at least 3 GTC seizures during the 8-week baseline phase in the first study pertains to patients with more severe GE.

*Clinical context*
Only high LEV doses were used.

*Recommendations*
For add-on therapy for GE, immediate-release and LTG-XR use should be considered as add-on therapy to decrease seizure frequency in treating adults with TR GTC seizures secondary to GE (Level B). Levetiracetam use should be considered to decrease seizure frequency as add-on therapy for TR GTC seizures and for TR JME (Level B).

*Clinical context*
Because the seizures of most patients with idiopathic GE are easily controlled with appropriate medication, presentation of TR epilepsy is rare. It is unclear how results in this population would translate to patients with similar syndromes but with nonrefractory disease.

### For adult and pediatric patients with LGS, are these AEDs effective as adjunctive therapy in reducing seizure frequency (compared with no adjunctive therapy)?

In the 2004 guidelines, FBM, LTG, and TPM were found to be effective in treating LGS. Since then, studies of CLB and RFN have been published.

**Clobazam**
CLB efficacy was compared with placebo in 2 Class II studies. Three daily doses (0.25, 0.5, and 1 mg/kg) were examined.[e5,e6] Relative to baseline seizure frequency, weekly drop seizure rates were significantly reduced with all 3 doses, with greater reduction in the high-dose group. Nondrop seizures were also reduced in a dose-dependent manner. The most common AEs included somnolence, lethargy, sedation, salivary hypersecretion, constipation, aggression, hypomania, and insomnia. Lethargy, aggression, ataxia, fatigue, and aggression were the most frequent AEs leading to drug discontinuation.

*Conclusion*
CLB is probably effective as add-on therapy for LGS (2 Class II studies).

**Rufinamide**
Two Class I studies compared RFN with placebo in children and young adults.[e7,e8] Doses up to 45 mg/kg/d were examined. Patients randomized to RFN experienced significantly greater median percent reductions in total seizure frequency and frequency of drop attacks and greater median percent change in tonic–atonic seizures. Common AEs included somnolence, vomiting, and decreased appetite.

*Conclusion*
RFN is established as effective as add-on therapy for LGS (2 Class I studies).

*Recommendations*
For LGS, RUF use should be considered established as effective to decrease seizure frequency as add-on therapy (Level A), and CLB use should be considered (Level B).

### For pediatric patients with TR focal epilepsy, are these AEDs effective as adjunctive therapy in reducing seizure frequency (compared with no adjunctive therapy)?

In the 2004 guideline, GBP, LTG, OXC, and TPM were found to be effective as add-on therapy in treating TR focal epilepsy in children. Since then, 4 studies have been published: 2 on LEV, 1 on OXC, and 1 on ZNS.

**Levetiracetam**
Two Class I studies compared LEV with placebo.[e9,e10] The first study[e9] included children and young adolescents (aged 4–16 years) and a target dose of 60 mg/kg/d. LEV had significantly greater responder rates per week and median reductions in seizure frequency per week. LEV was associated with more frequent AEs, which included somnolence, accidental injury, vomiting, anorexia, rhinitis, hostility, increased cough, pharyngitis, and nervousness. However, AE-related withdrawal from the study was higher among children randomized to placebo.

The second Class I study randomized children aged 1 month to <4 years to placebo or LEV at a dose of 40 mg/kg/d (if aged <6 months) or 50 mg/kg/d (if aged ≥6 months).[e10] Children randomized to LEV had a significantly greater responder rate in average daily seizure frequency and greater median percent reduction from baseline. The most frequently reported LEV-related AEs included somnolence and irritability.

*Conclusions*
LEV is probably effective as add-on therapy for TR focal epilepsy in children and adolescents (1 Class I study). Moreover, LEV is probably effective as add-on therapy in TR focal epilepsy in infants and children aged <4 years (1 Class I study).

**Oxcarbazepine**
One Class I study of children aged 1 month to <4 years compared 2 doses of OXC (10 mg/kg/d and 60 mg/kg/d).[e11] The primary outcome was absolute change in the frequency of focal seizures per 24 hours during 3 days of continuous treatment-phase video EEG compared with baseline seizure frequency. Children on the higher OXC dose experienced a significantly greater seizure frequency reduction and a greater median percent reduction in seizure frequency per 24 hours than those on the low dose. Children in the high-dose group also experienced more frequent AEs, including somnolence, ataxia, and vomiting.

### Conclusion

OXC is probably effective as add-on therapy in infants and young children with TR focal epilepsy (1 Class I study). Given the study's short duration, however, generalizability may be limited.

### Zonisamide

One Class I study of children and adolescents aged 6–17 years compared 8 mg/kg/d ZNS to placebo.[e12] The 12-week responder rate was significantly higher for the patients randomized to ZNS. The incidence of AEs did not differ between the 2 groups, although AEs leading to withdrawal occurred more often in the placebo group. The AEs reported with a higher frequency in the ZNS group included decreased appetite, decreased weight, somnolence, vomiting, and diarrhea.

### Conclusion

ZNS is probably effective as add-on therapy for TR focal epilepsy in children and adolescents (1 Class I study). Data are unavailable on the efficacy of CLB, ESL, LCM, PER, PGB, RFN, TGB, or VGB as add-on therapy for this group.

### Recommendations

For add-on therapy for TR focal epilepsy, LEV use should be considered to decrease seizure frequency (Level B for ages 1 month to 16 years), ZNS use should be considered to decrease seizure frequency (Level B for ages 6–17 years), and OXC use should be considered to decrease seizure frequency (Level B for ages 1 month to 4 years).

Data are unavailable on the efficacy of CLB, ESL, LCM, PER, PGB, RFN, TGB, or VGB as add-on therapy for the treatment of these children or adolescents (Level U).

### Clinical context

A pharmacokinetic: pharmacodynamic analysis performed comparing adults with children receiving approved AEDs showed similar seizure reduction for the 2 groups when serum concentrations were similar. On the basis of these data, the FDA determined that efficacy of AEDs for focal seizures in adults can be extrapolated downward to children 4 years of age.[e13,e14]

### For pediatric patients with TR focal epilepsy, are these AEDs effective as monotherapy in reducing seizure frequency?

No data are available to answer this question. Thus, no recommendation is made.

### Have new serious AEs been identified in the AEDs evaluated in the 2004 guideline?

No new serious AEs have been identified.

# Recommendations for future research

Head-to-head trials are lacking on newer AEDs in patients with TR focal epilepsy and TR GE. In studies of new-onset epilepsy, higher-dose forced titrations led to higher AE rates. Future studies should use doses commonly used in clinical practice and use flexible-dosing regimens. Finally, there is a lack of placebo-controlled and head-to-head trials of newer AEDs in pediatric patients.

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The American Academy of Neurology (AAN) and the American Epilepsy Society (AES) are committed to producing independent, critical, and truthful clinical practice guidelines (CPGs). Significant efforts are made to minimize the potential for conflicts of interest to influence the recommendations of this CPG. To the extent possible, the AAN and AES keep separate those who have a financial stake in the success or failure of the products appraised in the CPGs and the developers of the guidelines. Conflict of interest forms were obtained from all authors and reviewed by an oversight committee prior to project initiation. The AAN and AES limit the participation of authors with substantial conflicts of interest. The AAN and AES forbid commercial participation in, or funding of, guideline projects. Drafts of the guideline have been reviewed by at least 3 AAN committees, 3 AES committees, a network of neurologists, *Neurology* peer reviewers, and representatives from related fields. The AAN Guideline Author Conflict of Interest Policy can be viewed at aan.com. For complete information on this process, access the 2004 AAN process manual.[3]

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**Practice guideline update summary: Efficacy and tolerability of the new antiepileptic drugs II: Treatment-resistant epilepsy: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology and the American Epilepsy Society**

Andres M. Kanner, Eric Ashman, David Gloss, et al.

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## Generalized polyspike train

An EEG biomarker of drug-resistant idiopathic generalized epilepsy

*Neurology*® 2018;91:1117. doi:10.1212/WNL.0000000000006797

In the article "Generalized polyspike train: An EEG biomarker of drug-resistant idiopathic generalized epilepsy" by Sun et al.,[1] one author's name should read as Kee Meng Tan. The authors regret the errors.

### Reference

1. Sun Y, Seneviratne U, Perucca P, et al. Generalized polyspike train: an EEG biomarker of drug-resistant idiopathic generalized epilepsy. Neurology 2018;91:e1822–e1830.

## Novel biomarker signatures for idiopathic REM sleep behavior disorder

A proteomic and system biology approach

*Neurology*® 2018;91:1117. doi:10.1212/WNL.0000000000006791

In the article "Novel biomarker signatures for idiopathic REM sleep behavior disorder: A proteomic and system biology approach" by Mondello et al.,[1] the institution for Dr. Giuseppe Plazzi, Dr. Elena Antelmi, and Dr. Monica Moresco should read as the "University of Bologna and IRCCS Istituto delle Scienze Neurologiche di Bologna, Bologna, Italy." The authors regret the error.

### Reference

1. Mondello S, Kobeissy F, Mechref Y, et al. Novel biomarker signatures for idiopathic REM sleep behavior disorder: a proteomic and system biology approach. Neurology 2018;91:e1710–e1715.

## Practice guideline update summary: Efficacy and tolerability of the new antiepileptic drugs II: Treatment-resistant epilepsy

Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology and the American Epilepsy Society

*Neurology*® 2018;91:1117. doi:10.1212/WNL.0000000000006636

In the article "Practice guideline update summary: Efficacy and tolerability of the new anti-epileptic drugs II: Treatment-resistant epilepsy" by Kanner et al.,[1] there is an error in the abstract, which should have read "2004 criteria were used to *systematically* review literature" rather than "…systemically review…" as originally published. The authors regret the error.

### Reference

1. Kanner AM, Ashman E, Glass D, et al. Practice guideline update summary: efficacy and tolerability of the new antiepileptic drugs II: treatment-resistant epilepsy. Neurology 2018;91:82–90.