Practice guideline update: 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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DISCLOSURE
A. Kanner has served on a scientific advisory board for UCB but the honorarium was transferred to the Department of Neurology at the University of Miami, Miller School of Medicine; receives royalties from *Psychiatric Aspects of Epilepsy*, *Treatment of Depression in Neurological Disorders*, and *Psychiatric Controversies in Epilepsy*; and received honoraria from Medscape and as a consultant for Neuropace.

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D. Gloss serves as an evidence-based medicine consultant for the AAN.

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B. Abou-Khalil has served on but declined honoraria from scientific advisory boards for Sunovion and GlaxoSmithKline; served on the editorial board for *Epilepsy Research* and *Clinical Neurophysiology*; and received royalties for *Atlas of EEG & Seizure Semiology*. His institution received research support from UCB, GlaxoSmithKline, Valeant, Sunovion, Upsher-Smith, Pfizer, Cyberonics, and SK Life Science, from the NIH for the Epilepsy Phenome/Genome Project and from the Human Epilepsy Project.

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Monitoring; receives honoraria from and serves on the speakers bureaus of UCB, Lundbeck, Eisai, Cyberonics, and Sunovion; and performs clinical practice in epilepsy (50% of his time).

D. Hirtz reports no relevant disclosures.

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ABBREVIATIONS

AAN: American Academy of Neurology
AE: adverse event
AED: antiepileptic drug
CBZ: carbamazepine
CLB: clobazam
ESL: eslicarbazepine
EZG: ezogabine
FDA: Food and Drug Administration
FBM: felbamate
GBP: gabapentin
GE: generalized epilepsy
GTC: generalized tonic–clonic
JME: juvenile myoclonic epilepsy
LCM: lacosamide
LEV: levetiracetam
LEV-XR: extended-release levetiracetam
LGS: Lennox-Gastaut syndrome
LTG: lamotrigine
LTG-IR: immediate-release 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
REMS: risk evaluation and mitigation strategy
RFN: rufinamide
RTC: randomized controlled trial
SAE: serious adverse event
TGB: tiagabine
TPM: topiramate
TPM-XR: extended-release topiramate
TR: treatment resistant
TRAFE: treatment-resistant adult focal epilepsy
VGB: vigabatrin
VPA: valproate
ZNS: zonisamide

ABSTRACT

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

Methods: A guideline panel systematically reviewed literature review from January 2003 to November 2015 (the previous guideline covered literature from 1987–2003); classified pertinent studies according to the AAN therapeutic scheme; and tied recommendations to evidence strength. Six questions were asked regarding the effectiveness and tolerability of these AEDs as adjunctive therapy and monotherapy in treating TR focal epilepsy and generalized epilepsy (GE) and as add-on therapy in treating Lennox–Gastaut syndrome (LGS). One question addressed serious adverse events.

Results and recommendations: Forty-two articles were reviewed. For adults with TR focal epilepsy, immediate-release pregabalin, and perampanel have established efficacy and should be considered first-line therapy to reduce seizure frequency (Level A). Lacosamide, eslicarbazepine, and extended-release topiramate should also be considered for use to decrease seizure frequency in this population (Level B). Vigabratin and rufinamide should be considered established as effective for decreasing seizure frequency in adults with TR focal epilepsy (Level A), but they are not first-line agents (retinopathy risk with vigabratin and modest benefit with rufinamide). Ezogabine could have been considered appropriate for use to decrease seizure frequency in this population (Level B), but it carries a serious risk of skin and retinal discoloration and it is no longer in production. Clobazam and extended-release oxcarbazepine may be considered for use to decrease seizure frequency in adults with TR focal epilepsy (Level C). For monotherapy use in adults with TR focal epilepsy, eslicarbazepine may be considered for use to decrease seizure frequency as monotherapy for adults with TR focal epilepsy (Level C). For add-on therapy for GE, immediate- and extended-release lamotrigine should be considered for use to decrease seizure frequency in treating adults with TR generalized tonic–clonic (GTC) seizures secondary to GE (Level B). Levetiracetam should be considered for use to decrease seizure frequency as add-on therapy for both TR GTC seizures and TR juvenile myoclonic epilepsy (Level B). For LGS, rufinamide should be considered established as effective to decrease seizure frequency as add-on therapy for TR focal epilepsy (Level A), whereas clobazam should be considered for use (Level B). For add-on therapy for patients with TR focal epilepsy, levetiracetam should be considered for use to decrease seizure frequency (Level B ages 1 month to 16 years); zonisamide should be considered for use to decrease seizure frequency (Level B ages 6 to 17 years), and oxcarbazepine should be considered for use to decrease seizure frequency (Level B ages 1 month to 4 years). AED choice depends on seizure type or syndrome type (or both), patient age, concomitant medications, and AED tolerability, safety, and efficacy. Notably, a recent FDA strategy allows extrapolation of efficacy across populations; therefore, eslicarbazepine and lacosamide (oral only for pediatric age group) received FDA approval for treatment of focal epilepsy as add-on or monotherapy in persons aged 4 years and older, and perampanel received FDA approval for monotherapy for focal epilepsy.

INTRODUCTION

Approximately 30%–40% of patients with epilepsy continue to experience seizures despite multiple trials with antiepileptic drugs (AEDs). Two practice guidelines, 1 on felbamate (FBM)[e1] and another on 7 newer (all referred to as second-generation) AEDs (gabapentin [GBP], lamotrigine [LTG], levetiracetam [LEV], oxcarbazepine [OXC], tiagabine [TGB], topiramate [TPM], and zonisamide [ZNS]),[e2] found all 8 drugs to be effective as add-on therapy in adults with treatment-resistant (TR) focal epilepsy, whereas LTG, OXC, and TPM were each found to be effective as monotherapy. GBP, LTG, OXC, and TPM were found to be effective as add-on therapy in children with TR focal epilepsy. In addition, FBM, LTG, and TPM were found to be effective as add-on therapy in children and adults with Lennox–Gastaut syndrome (LGS). Table e-1 summarizes the most relevant findings of these guidelines.

Since the 2004 guideline publications, the US Food and Drug Administration (FDA) has approved 6 new drugs, now referred to as third-generation AEDs that are included in this update (eslicarbazepine [ESL], ezogabine [EZG], lacosamide [LCM], perampanel [PER] pregabalin [PGB], and rufinamide [RFN]) and 2 older AEDs (clobazam [CLB] and vigabatrin [VGB]), for treating certain types of seizure disorders. The identified mechanisms of action of these 8 AEDs are summarized in table e-2, their common and serious adverse events (SAEs) in table e-3, and the clinically relevant pharmacokinetic properties in table e-4. The FDA also approved an additional new drug, brivaracetam, and an additional indication for perampanel (for primary generalized tonic clonic seizures)since the 2004 guideline that are not included in this update. These were excluded since 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.

In this update, the guideline panel reviews new evidence for the efficacy, safety, and tolerability of the 8 second- and 6 third-generation AEDs in managing TR focal epilepsy and generalized epilepsy (GE) in children and adults.

In addition to considering the recently approved AEDs previously listed, this update reviews new evidence regarding the AEDs assessed in the 2004 guideline. The following questions are addressed:

1. For adult patients with TR focal epilepsy, are these AEDs effective as adjunctive therapy in reducing seizure frequency (compared with no adjunctive therapy)?
2. For adult patients with TR focal epilepsy, are these AEDs effective as monotherapy in reducing seizure frequency?
3. For adult and pediatric patients with TR GE, are these AEDs effective as adjunctive therapy in reducing seizure frequency (compared with no adjunctive therapy)?
4. For adult and pediatric patients with LGS, are these AEDs effective as adjunctive therapy in reducing seizure frequency (compared with no adjunctive therapy)?
5. For pediatric patients with TR focal epilepsy, are these AEDs effective as adjunctive therapy in reducing seizure frequency (compared with no adjunctive therapy)?
6. For pediatric patients with TR focal epilepsy, are these AEDs effective as monotherapy in reducing seizure frequency?
7. Have new SAEs been identified in the AEDs evaluated in the 2004 guideline?

In this guideline update, new studies of the AEDs reviewed in the previous guidelines were included if they resulted in a treatment recommendation (Level A, B, or C). For the third-generation AEDs not reviewed in the previous guidelines, the panel included studies with a Class I, II, or III rating.

DESCRIPTION OF THE ANALYTIC PROCESS

The American Academy of Neurology (AAN) guideline subcommittee and the American Epilepsy Society assembled an author panel of adult and pediatric epileptologists, methodologic experts, doctors of pharmacology, and general neurologists to review the evidence (appendices e-1 through e-3). The panel used the AAN 2004 Clinical Practice Guideline Process Manual[e3] in the development of this update. New studies were identified through computerized searches of the MEDLINE, EMBASE, Scientific Citation Index (using Web of Science), and Cochrane databases. An initial search was conducted from January 2004 to March 2009 for the 8 AEDs reviewed in the 2004 guidelines and the newer AEDs approved since the 2004 publications. A second search was conducted to include studies published to November 2015. For CLB and VGB, a search was conducted from 1980 to 2014. See appendix e-4 for the search strategy.

Studies on the efficacy of AEDs were included if they were published in English and involved at least 20 patients. In the assessment of SAEs, case reports and case series of fewer than 20 patients were accepted. Two panel members reviewed the studies independent of each other using the 2004 AAN therapeutic classification of evidence scheme (appendix e-5). Differences in ratings were resolved by discussion between the 2 panel members and, if needed, arbitration by an independent third reviewer. Class IV articles were not reviewed for evidence but may have been included if important adverse events (AEs) were identified. For each study, the guideline panel identified the most frequent AEs and the AEs leading to discontinuation from the trial. Recommendations were linked to the strength of the evidence (appendix e-6). In a companion guideline,[e4] the guideline panel updated the evidence regarding efficacy and tolerability of these AEDs in the treatment of new-onset focal epilepsy or generalized epilepsy.

ANALYSIS OF EVIDENCE

Question 1: For adult patients with TR focal epilepsy, are these AEDs effective as adjunctive therapy in reducing seizure frequency?

Pregabalin

The guideline panel identified 5 multicenter, double-blind, randomized controlled trials (RCTs): 2 Class I and 2 Class II on immediate-release PGB (PGB-IR) and 1 Class I on controlled-release PGB (PGB-CR).

One Class I study compared placebo with 4 doses of PGB (50, 150, 300, and 600 mg/d, in twice-per-day dosing) in 453 patients.[e5] The second Class I study compared placebo with 2 doses of PGB (150 vs 600 mg/d in a 3-times-per-day dosing) in 288 patients.[e6] A Class II study compared the efficacy and tolerability of placebo with 2 PGB regimens[e7]: 1 regimen of a fixed dose of 600 mg/d and 1 regimen of flexible doses (150–600 mg/d). The second Class II study also compared placebo with PGB at 600 mg/d on a twice-per-day vs 3-times-per-day regimen.[e8] With the exception of the 50-mg/d dose in the first Class I study, every tested dose of PGB was significantly superior to placebo for higher responder rates (> 50% reduction in seizure

frequency) and greater median percent seizure reduction, all in a dose-related manner. There was no difference in the efficacy and tolerability of PGB taken on a twice-per-day or 3-times-per-day schedule.

Dizziness and sedation were the most frequently occurring AEs; the frequency was dose dependent. Dose dependent weight gain also occurred: 12.4% of patients on 600 mg/d had a mean weight gain of 2.28 kg. Drug discontinuation due to AEs was also dose related and mostly from dizziness and sedation.

A Class I multicenter double-blind RCT in 330 patients compared the efficacy and tolerability of placebo with 2 once-a-day doses of PGB-CR, 165 mg/d and 330 mg/d.[e9] The 3 treatment arms failed to differ in the primary outcome ($\log_e$-transformed 28-day seizure-rate); a high placebo response contributed to this finding. AEs and AE-related discontinuation rates were similar to those of trials of PGB-IR and were more frequent in patients randomized to the higher dose of PGB-CR .[e6–e8]

Conclusions
PGB-IR is effective as add-on therapy for TR focal epilepsy (2 Class I and 2 Class II studies). Efficacy and AEs increase with higher doses. PGB-CR is probably not effective at 165- and 330-mg doses (1 Class I study).

Clinical context
In the studies using PGB-IR , starting doses were higher than those currently used in clinical practice (25–50 mg/d) and may have led to higher AE occurrence rates.

The lack of efficacy of PGB-CR compared with placebo may be owing to an exceptionally high placebo responder rate or the failure to use maximal doses (e.g., 600 mg/d).

The FDA designated PGB as a Schedule V controlled substance because of reports of euphoric mood in a minority of patients with a history of drug abuse.

Lacosamide
Three multicenter double-blind RCTs (1 Class I and 2 Class II) were identified.[e10–e12] The Class I study compared the efficacy and tolerability of LCM at 200 and 400 mg/d with those of placebo in 485 patients aged 16–70 years.[e10] One Class II study compared the efficacy of placebo and LCM at doses of 400 and 600 mg/d in 405 patients.[e11] The second Class II study compared placebo with LCM at doses of 200, 400, and 600 mg/d.[e12] LCM at doses of 400 and 600 mg/d showed significantly higher responder rates and greater median reduction of seizures than placebo. LCM at 600 mg/d was not more effective for focal seizures with associated loss of awareness than 400 mg/d in any study. In 1 Class II study,[e11] reductions in secondarily generalized tonic–clonic (GTC) seizures were obtained on the higher dose.

Discontinuations due to AEs were dose dependent. In the Class I study,[e10] discontinuation occurred more frequently during the titration period. The most frequent AEs included diplopia, vertigo, and emesis. Dizziness, nausea, fatigue, ataxia, diplopia, nystagmus, headaches, and abnormal coordination were common dose dependent AEs in all 3 studies.

Safety of the parenteral form of LCM was assessed in a Class III multicenter, open-label, inpatient trial, with 160 patients on stable doses of oral LCM ranging from 200–800 mg/d.[e13] These patients were converted to the same doses intravenously infused over 10, 15, and 30 minutes for 2–5 days. Headache, dizziness, and somnolence were the most common AEs, for which frequency increased at doses > 400 mg/d but were unaffected by shorter infusion times or increased exposure days.

Conclusion
LCM is probably effective in adults with TR focal epilepsy (1 Class I study and 2 Class II studies).

Clinical context
The starting doses were higher than those currently used in clinical practice (50–100 mg/d) and may have led to a higher AE occurrence rate. Furthermore, a review of the pooled data of the LCM studies suggests the prevalence of dizziness was twice as frequent when LCM was used with other sodium channel drugs (carbamazepine [CBZ], LTG, OXC).[e14]

The FDA designated LCM as a Schedule V controlled substance because of reports of euphoric mood in a minority of patients with a history of drug abuse.

Rufinamide
Three double-blind RCT Class I multicenter studies were identified.[e15–e17] Two studies compared the efficacy and tolerability of RFN at a dose of 3,200 mg/d with those of placebo in 312 patients aged ≥16 years and in 357 patients aged 12–80 years, respectively.[e15,e17] In the second study, 647 patients unable to tolerate the target dose could have their dose reduced to 2,400 mg during the titration phase only.[e17] The third study compared the efficacy and tolerability of placebo and 4 doses of RFN (200, 400, 800, and 1,600 mg) in 647 patients aged 15 years and older.[e16] All study doses were compared with placebo. RFN was superior to placebo for median reduction of seizure frequency per 28 days and responder rate. The third study[e16] showed 400 mg/d was the lowest effective dose for both outcome measures. Of note, while the differences in both efficacy outcomes reached statistical significance in all 3 studies, the magnitude of improvement was modest.

The most frequent AEs in the 3 studies were dizziness, fatigue, nausea, somnolence, diplopia, confusion, ataxia, and impaired concentration. The discontinuation rate was higher among patients randomized to RFN. In one study,[e16] AEs were more frequent only at doses of 1,600 mg/d compared with the other doses and placebo and were similar in type to those found in the other 2 studies.

Conclusion
RFN is effective as add-on therapy for TR focal epilepsy, but reported benefits were modest (3 Class I studies).

Ezogabine

Three double-blind RCT Class II studies[e18–e20] were identified. In the first study, the efficacy and tolerability of placebo and EZG at 600 mg/d and 900 mg/d were compared in 538 patients.[e18] The second study compared 3 EZG doses (600 mg/d, 900 mg/d, and 1,200 mg/d) and placebo in 399 patients.[e19] In the third study, patients were randomized to placebo or EZG at 1,200 mg/d.[e20] Each EZG dose was superior to placebo with respect to median percent seizure reduction and responder rates.

In all studies, AEs were the most frequent cause of drug discontinuation and occurred in a dose dependent manner. In the first study,[e18] the most frequent AEs included dizziness, somnolence, headache, and fatigue, and the most common AEs resulting in discontinuation were dizziness and somnolence. In the second study,[e19] the most common AEs occurred during the titration phase, accounted for 91% of all discontinuations, and were confusion, speech disorder, dizziness, and somnolence in the treatment arm and confusion in the placebo arm. Other common AEs included vertigo, tremor, amnesia, abnormal thinking, abnormal gait, paresthesia, and diplopia. AEs identified in the third study[e20] were the same as those cited in the 2 other studies. Encephalopathic states reported as confusional episodes (seen in 14% vs 1% on placebo) and disorientation (5% vs 1% on placebo) were identified. Psychiatric AEs included anxiety in 5% of patients on EZG (vs 3% on placebo), hallucinations in 2%, and visual hallucinations in 3% (vs 0% on placebo). A mean 3.5% body weight increase was identified in patients on EZG (vs 0.4% on placebo). Eighteen-and-one-half percent of patients on EZG had weight gain of ≥7% (vs 3.1% for placebo).

One Class III multicenter double-blind RCT enrolled 73 patients (aged 16–70 years old) comparing the safety and tolerability among 3 titration regimens, fast, medium, and slow, consisting of 150-mg increments every 2, 4, and 7 days, respectively, with a starting daily dose of 300 mg/d and a target dose of 1,200 mg/d.[e21] A significantly higher prevalence of AEs was identified in patients randomized to the fast titration rates. The type of AEs was similar to those reported in the 3 studies cited in the previous paragraph.[e18–e20]

Conclusion
EZG is probably an effective add-on therapy for TR focal epilepsy in adults (3 Class II studies).

Clinical context
In April 2013, the FDA issued a warning indicating that EZG can cause blue skin discoloration and eye abnormalities (characterized by pigment changes in the retina). The FDA had no available data to establish whether these changes were reversible. Accordingly, the FDA recommended that any patient taking EZG have a baseline assessment and periodic eye examinations that should include visual acuity testing and dilated fundus photography. Fluorescein angiograms, ocular coherence tomography, perimetry, and electroretinograms were also surveillance options. The FDA suggested EZG should be discontinued if ophthalmic changes are observed, unless no other treatment options are available. A change to another AED was strongly recommended if patients experienced skin discoloration.

Urinary retention had been identified in patients taking EZG. This is attributed to the drug's activation of potassium channels in the urothelium of the bladder. Accordingly, an FDA Risk Evaluation and Mitigation Strategy (REMS) had been put in place for urinary retention risk and

symptoms. Further, the FDA designated EZG as a Schedule V controlled substance because of reports of euphoric mood in a minority of patients with a history of drug abuse.
Because of the presence of psychiatric AEs, confusional episodes, the risk of skin and retinal discoloration, and risk of bladder retention, EZG should not be considered a first-line drug. As of June 2017, the manufacturer of EZG has discontinued production of the drug.

Vigabatrin
Two double-blind Class I RCTs were identified.[e22,e23] In one study,[e22] the efficacy and tolerability of VGB at a 3-g/d dose was compared with placebo in 182 patients. In the second study, 174 patients were randomized to placebo or 1 of 3 VGB doses (1 g/d, 3 g/d, or 6 g/d).[e23] In both studies, all VGB doses resulted in significantly higher responder rates and median reduction in monthly seizure frequency. The second study demonstrated a dose dependent advantage of VGB over placebo in both efficacy variables.[e23]

In both studies, fatigue and drowsiness were the most frequent AEs, which resulted in a greater number of drug discontinuations in the 6-g/d group. Psychiatric AEs also resulted in drug discontinuation, mostly owing to depression and irritability in a dose-related manner.[e23] Of note, more psychiatric SAEs have been reported in patients with a prior psychiatric history.[e24]

In 1997, 7 years after European VGB approval, serious irreversible retinopathies were identified, resulting in bilateral concentric constriction of the visual field, affecting more often the nasal visual fields. A meta-analysis of 32 studies totaling 1,678 patients exposed to VGB and 406 controls revealed visual field loss in 738 patients (44%) and 30 controls (7%), yielding a relative risk for field loss of 4.0 (95% CI 2.9–5.5).[e25] Higher cumulative doses of VGB and increasing age were associated with a higher proportion of patients with visual field loss. Patients are required by the FDA's REMS to undergo visual field examinations every 3 months.

Conclusion
VGB is effective as add-on therapy in TR focal epilepsy (2 Class I studies).

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

Clobazam
CLB is an AED of the benzodiazepine family, which has been used for treating epilepsy since 1979 in Canada, Europe, and Latin America. There were 3 Class III studies available for review, and all were randomized, double-blind, crossover, placebo-controlled trials.[e26–e28] The only multicenter trial included 129 patients, of whom 29 had GE[e24]; the CLB doses ranged from 10–40 mg/d. Patients randomized to CLB had significantly greater reductions in seizure frequency than placebo, and 19 patients on CLB became seizure free vs none on placebo. The second and third studies[e26,e27] included 20 and 26 patients, respectively (in the latter study, 6 patients had GTC seizures); CLB doses were 40 mg/d and 30 mg/d, respectively. In the second study, CLB yielded significantly greater reductions in the mean number of seizures per month. In the third study, there was a significantly greater seizure reduction and responder rate with CLB.

In the 3 studies, AEs were more frequent in patients taking CLB and included sedation, dizziness, irritability, depression, and disinhibition.

Conclusion
CLB is possibly effective as add-on therapy for TR focal epilepsy (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
Three Class I multicenter double-blind RCTs on PER were conducted in a combined total of 1,399 patients (386 in the first study, 390 in the second study, and 623 in the third study) aged 12 years and older.[e29–e31] Two studies[e29,e30] compared the efficacy and tolerability of 2 PER doses (8 mg/d and 12 mg/d) with placebo and differed only in that PER was given as a single daily dose in the first study and twice daily in the second. The third study compared the efficacy and tolerability of 3 PER doses (2 mg/d, 4 mg/d, and 8 mg/d) with placebo. PER doses of 4, 8, and 12 mg/d were superior to placebo with respect to median percent reduction in seizure frequency per 28 days.[e29,e30] In the first 2 studies, no significant differences were found between 8- and 12-mg doses, and in the third study, there was a significant difference favoring the 8-mg/d dose when compared with 2- and 4-mg/d doses. The 50% responder rate was significantly higher for patients randomized to 8- and 12-mg/d doses compared with placebo in the first study[e29] but failed to differ between the 2 PER doses.[e29,e30] There were no significant differences between the 2 PER doses and placebo in the second study, but when the data analysis was restricted to patients from North American sites, the 50% responder rate was significantly higher for patients randomized to either dose than to placebo.[e30] Reasons for the geographical differences in the 50% responder rate were unclear. In the third study, the responder rate was significantly higher for patients randomized to 8 mg/d than 4 mg/d and placebo.[e31]

The most common AEs identified in the 3 studies were similar and included dizziness, ataxia, falls, headache, somnolence, fatigue, irritability, depression, nausea, and weight gain; these were dose related. AEs occurred during both the titration and maintenance phases. In all studies, drug discontinuation, dose adjustment, or dose interruption were more frequent among patients on PER and were also dose related.

Conclusion
PER is established as effective as add-on therapy in TR focal epilepsy (3 Class I studies).

Clinical context
The occurrence of psychiatric AEs associated with PER prompted a warning in the package insert. Among the 3 studies, 4 (0.9%) and 12 (1.2%) patients randomized to placebo and PER, respectively, experienced a psychiatric SAE, with aggression being the most common. There was a clear dose-related occurrence of depression (0.6% in patients on 4 mg/d and 2.4% in patients taking 12 mg/d [vs 1.6% of patients on placebo]) and aggression (0.6% of patients on 4 mg/d, and 3.1% of patients on 12 mg/d [vs 0.5% on placebo] with a higher rate in adolescents [7.8%] than adults [1.3%]).

Eslicarbazepine

Three multicenter double-blind RCTs (1 Class I, 1 Class II, and 1 Class III) were identified. In the Class I study,[e32] 402 patients were randomized to ESL 400 mg, ESL 800 mg, ESL 1,200 mg, or placebo. In the Class II study,[e33] 252 patients were randomized to ESL 800 mg, ESL 1,200 mg, or placebo. The Class III study randomized 395 patients to ESL 400 mg, ESL 800 mg, ESL 1,200 mg, or placebo.[e34] A single daily dose was used in all 3 studies. ESL doses of 800 mg and 1,200 mg were shown to significantly reduce the seizure frequency per 4-week period and yielded a significantly higher 50% responder rate in the Class I and Class III studies, but not in the Class II study. In the Class I study, the number of patients who became seizure free was also higher for the 1,200-mg dose. Of note, over half of the patients in each study were on CBZ during these trials.

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

Conclusion
ESL at 800 mg and 1,200 mg once per day is probably effective in TR focal epilepsy (1 Class I study, 1 Class II study, and 1 Class III study).

Clinical context
The Class I study may have limited generalizability because 100% of patients were Caucasian and the other 2 studies had mixed patient populations. Tolerability may have been affected by the fact that in all 3 studies more than 50% of patients were concurrently on CBZ, which is chemically related to ESL.

Extended-release OXC
Among the second-generation AEDs, 1 Class II study investigated the efficacy, safety, and tolerability of the extended-release formulation of OXC (OXC-XR).[e35] The international double-blind, multicenter, randomized, parallel study included 366 patients aged 18–65 years old randomized to placebo, OXC-XR 1,200 mg/d, or OXC-XR 2,400 mg/d as single daily doses. Of the 366 patients, 248 (67.8%) completed the treatment phase. Significant differences between OXC-XR and placebo were achieved only with the 2,400-mg/d dose in both the responder rate and the median percent seizure rate reduction. When the analysis was restricted to sites in North America, however, significant differences were identified in both outcome measures for the 1,200-mg/d and 2,400-mg/d doses, as placebo rates outside the United States were very high.

The most frequent AEs, including those leading to drug discontinuation, consisted of dizziness, ataxic gait, nausea, vomiting, headache, somnolence, fatigue, and diplopia.

Conclusion
OXC-XR is possibly effective for the treatment of TR focal epilepsy at a dose of 2,400 mg/d (1 Class II study).

Clinical context
The findings for the 1,200-mg/d dose may have been confounded by limited geographic analysis (data from the North American centers only).

Extended-release topiramate

The efficacy and safety of the extended-release formulation of TPM (TPM-XR) was studied in 1 Class I randomized, double-blind, multicenter, placebo-controlled trial of 249 adults (aged 18–75 years old) with TR focal epilepsy, given once daily at a dose of 200 mg/d.[e36] The primary outcome was the median percent reduction in weekly focal seizures and responder rate during the 11-week trial (3-week titration and 8-week maintenance periods). TPM-XR was superior to placebo with respect to both outcome variables.

The most frequent AEs reported among patients randomized to TPM-XR were somnolence, paresthesia, and weight loss. Discontinuation due to AEs was more frequent in patients randomized to TPM-XR (9.7%) than placebo (3%).

Of note, as of this writing the FDA has approved 2 extended-release formulations of this AED, but this Class I study is the only published study.

Conclusion

TPM-XR is probably effective as add-on therapy for adults with TR focal epilepsy (1 Class I study).

Recommendations

For adults with TR focal epilepsy, PER and PGB-IR have established efficacy to reduce seizure frequency (Level A). ESL, LCM, 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 adults with TR focal epilepsy (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 adults with TR focal epilepsy (Level C).

Question 2: For adult patients with TR focal epilepsy, are these AEDS effective in reducing seizure frequency when used as monotherapy?

In the 2004 guideline,[e2] LTG, OXC, and TPM were 3 second-generation AEDs found to be effective as monotherapy for the treatment of TR focal epilepsy in adults. Since then, 5 conversion-to-monotherapy trials were published: 1 on a second-generation AED (extended-release LEV [LEV-XR]),[e37] and 4 on third-generation AEDs (1 study on PGB[e38], 1 on LCM,[e39] and 2 on ESL).[e40,e41] This study design is used because standard placebo-controlled monotherapy trials cannot be performed in this population because of risk of seizures on placebo. In all 5 studies, the primary efficacy variable consisted of a cumulative exit rate at day x (based on a predefined exit criteria, which indicate worsening during conversion) compared with a historical control.

Extended-release LEV

The study on LEV-XR consisted of a Class III multicenter, double-blind, conversion-to-monotherapy RCT, which included 228 patients (aged 12–75 years old) who were taking 1 or 2 AEDs.[e34] One hundred seventy-one patients were randomized to 2,000 mg/d (efficacy group) and

57 patients to 1,000 mg/d (safety group) taken once daily. The LEV-XR dose was titrated over a 2-week period, the concomitant AEDs were tapered down over a 6-week period, and efficacy in monotherapy was established over a 10-week period. The cumulative exit rate at day 112 was significantly lower for patients randomized to high-dose LEV-XR than that of historical controls. The most frequent AEs included somnolence, headaches, and convulsions and failed to differ between the 2 doses.

Pregabalin

The Class III multicenter, double-blind, conversion-to-monotherapy RCT on PGB included 161 patients (aged ≥18 years) who were taking 1 or 2 AEDs.[e38] Patients were randomized to 600 mg/d and 150 mg/d titrated over a 2-week period, the concomitant AEDs were tapered down over an 8-week maintenance period, and the efficacy was established over a 12-week period. The trial was stopped early after positive efficacy was demonstrated following an interim analysis in 125 patients, as the predicted exit rate for the 600-mg/d group was significantly lower than that of the historical control threshold. The most frequent AEs were similar to those reported in the add-on PGB trials discussed for question 1.[e6–e8]

Lacosamide

The Class III multicenter, double-blind, conversion-to-monotherapy RCT[e39] on LCM enrolled 425 patients (aged 16–70 years) who were taking 1 or 2 AEDs. Patients were randomized to LCM 300 mg/d and 400 mg/d titrated over a 3-week period, while the concomitant AEDs were tapered down over a 6-week period, and the efficacy was established with the 400-mg/d group over a 16-week maintenance period. The predicted exit percentage at day 112 was significantly lower than that of the historical control. The most frequent AEs included dizziness, headache, nausea, convulsions, somnolence, and fatigue, most of which were of mild to moderate severity. The prevalence of dizziness was higher in the 400-mg/d group, but that of the other AEs did not differ between the 2 doses. LCM was discontinued by 16.9% of patients because of AEs, and SAEs were identified in 4% of patients, all of whom were taking 400 mg/d.

Eslicarbazepine

Two Class III multicenter, double-blind, conversion-to-monotherapy RCTs[e40,e41] on ESL enrolled 195 and 172 patients, respectively (aged 16–70 years old), who were taking 1 or 2 AEDs. Patients were randomized to 1,200 mg/d and 1,600 mg/d titrated over a 2-week period, while the concomitant AEDs were tapered down over a 6-week period, and the efficacy was established at the 10-week maintenance period. In both studies, the predicted exit percentage at day 112 was significantly lower than that of the historical control. The most frequent AEs included headache, nausea, back pain, dizziness, and pharyngitis, most of which were of mild to moderate in severity and occurred in a dose dependent manner. Hyponatremia was identified in 6.7% one study 39 and accounted for the most frequent cause of AE-related discontinuation. The prevalence of AEs was higher during the titration period and in the 1,600-mg/d group.

Conclusions

ESL is possibly effective as monotherapy for TR focal epilepsy (2 Class III studies on ESL). Data are insufficient to establish efficacy of LCM, LEV-XR, or PGB as monotherapy for TR focal epilepsy (3 Class III studies, one on each of these drugs). No new Class I, II, or III studies have been published on CLB, EZG, GBP, PER, RFN, TGB, VGB, or ZNS.

Recommendations
ESL use may be considered to decrease seizure frequency as monotherapy for adults with TR focal epilepsy (Level C). No new evidence is available on the use of any second- or any of the other third-generation AEDs as monotherapy in adults with TR focal epilepsy (Level U).

Clinical context
The studies performed to demonstrate effectiveness of new AEDs in monotherapy in patients with refractory focal seizures are difficult to interpret because they are driven by FDA requirements to show superiority to placebo, pseudoplacebo, or historical control rather than by clinical questions. Dosages used in the trials are often higher than those that might be used in practice because the goal is to retain as many patients as possible and achieve a significant result. Most important, the goal of these studies is not to determine whether patients improve after they are converted to monotherapy but, rather, to determine whether their condition deteriorates to a lesser degree than that of the comparison group.

A white paper published in 2015 suggested that monotherapy efficacy can be extrapolated from efficacy in add-on studies, as long as no pharmacokinetic interaction is.[e42]

For adult and pediatric patients with TR GE, are these AEDs effective in reducing seizure frequency when used as adjunctive therapy in reducing seizure frequency (compared with no adjunctive therapy)?
In the 2004 practice guidelines, only TPM was found to be effective as add-on therapy in TR GTC seizures in adults and children. Since then, 3 LTG[e43–e45] and 2 LEV[e46,e47] studies have been identified.

Lamotrigine
One Class II multicenter, randomized, double-blind, placebo-controlled trial was conducted in 117 patients aged 2–55 years to treat GTC seizures.[e43] LTG titration was carried out over 12 weeks, and, for children aged <12 years, the dosage started at 0.3 mg/kg/d, 0.15 mg/kg/d if taking valproate (VPA), and 0.6 mg/kg/d if taking an enzyme-inducing AED, with maximal target doses being 5.4 mg/kg/d, 2.8 mg/kg/d, and 10.8 mg/kg/d, respectively. In patients older than 12 years, the initial doses were 25, 12.5 mg/d if taking VPA, 50 mg/d if taking an enzyme-inducing AED, and 25 mg/d if taking other AEDs, with maximal doses consisting of 300 mg/d, 150 mg/d, and 200 mg/d, respectively. Median percent reduction of GTC seizure frequency and responder rates during the entire study and the maintenance phase were significantly higher among patients randomized to LTG than placebo. The most common LTG-related AEs included dizziness, somnolence, and nausea.

A subsequent analysis of the data obtained from 45 children and adolescents aged 2–19 years included in that trial led to a second Class II study,[e44] which demonstrated significant differences in median percent decrease from baseline in GTC seizures both during the entire treatment period favoring LTG and during escalation and maintenance periods. Among the children randomized to LTG, 48% reached seizure freedom (compared with 17% treated with placebo) during the maintenance phase. AEs leading to drug discontinuation were rare (1 patient from each treatment group) and consisted of "disorientation" in the child treated with LTG. No rashes were reported in any patient.

Similar findings were obtained in a Class I multicenter RCT[e45] using the extended-release formulation of LTG (LTG-XR) in 153 patients aged ≥13 years. Compared with patients randomized to placebo, 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 (LTG-IR) are probably effective as add-on therapies for TR GTC seizures (1 Class I study on LTG-XR and 2 Class II studies on LTG-IR).

Levetiracetam
Two Class I studies have been published on the efficacy of LEV in TR GE, 1 including patients with only GTC seizures[e46] and the other including patients with juvenile myoclonic epilepsy (JME).[e47] The first study was a multicenter double-blind RCT comparing the efficacy and tolerability of LEV 3,000 mg/d with that of placebo in patients aged 4–65 years with ≥3 GTC seizures during an 8-week baseline period.[e46] All outcome variables favored the LEV treatment arm, including a significantly greater mean reduction in GTC seizure frequency per week, a significantly greater responder rate of seizure frequency per week, and a significantly greater proportion of patients attaining seizure freedom. The most common LEV-related AEs consisted of psychiatric symptoms (particularly irritability), fatigue, somnolence, and headache. More patients on placebo discontinued therapy because of AEs (4.8%) than on LEV (1.3%).

The second study was a multicenter double-blind RCT that included 120 patients aged 12–65 years with JME (93.6%) or juvenile absence epilepsy (6.6%) who experienced myoclonic seizures during ≥8 days in the course of a prospective 8-week baseline period.[e47] Sixty-one patients were randomized to 3,000 mg/d LEV, and 60 patients were randomized to placebo. A significantly greater number of patients on LEV had a > 50% reduction in the number of days per week with myoclonic seizures than those on placebo and became free not only of myoclonic seizures but also of any other seizure type. In this study, somnolence and neck pain were the only 2 AEs seen with greater frequency among patients on LEV than placebo.

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

Clinical context
Only high doses of LEV were used.

Recommendations
For add-on therapy for GE, immediate- and extended-release LTG should be considered for use as add-on therapy to decrease seizure frequency in adults with TR GTC seizures secondary to GE (Level B). LEV should be considered for use 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 practice guidelines, FBM, LTG, and TPM were found to be effective in treating LGS. Studies of CLB and RFN have been published since then.

Clobazam
Two Class II multicenter, randomized, double-blind, dose-ranging studies were available for review.[e48,e49] The first study compared CLB 0.25 mg/kg/d and 1.0 mg/kg/d as adjunctive therapy for drop seizures in 68 patients aged 2–26 years with LGS.[e48] Compared with baseline seizure frequency, weekly drop seizure rates were significantly reduced with both doses, with greater reduction in the high-dose group. A significantly greater proportion of patients in the high-dose group experienced drop seizure reduction rates by ≥25%, ≥50%, and ≥75% (compared with those in the low-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. The frequency and severity of these AEs were comparable between the 2 doses. Ten patients withdrew, 9 because of AEs (3 in the low-dose group and 6 in the high-dose group).

Similar findings were identified in the second study, which compared the efficacy and tolerability of placebo and CLB at doses of 0.25, 0.5, or 1.0 mg/kg/d in 157 patients aged 2–60 years, of whom 125 (79.6%) were completers.[e49] The average weekly reduction in the frequency of drop seizure rates and responder rates was significantly higher for all CLB doses in a dose dependent manner. For nondrop seizures, a significant difference in the reduction of seizures was identified only between patients on 1 mg/kg/d (using the rank-transformed percentage decrease in weekly rates of nondrop seizures). The most frequent AEs reported for CLB included somnolence, fever, upper respiratory infections, and lethargy; moreover, lethargy, aggression, ataxia, fatigue, and aggression accounted for the most frequent AEs leading to CLB discontinuation.

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

Rufinamide
Two Class I studies were available for review.[e50,e51] The first was a multicenter double-blind RCT comparing the efficacy and tolerability between RFN and placebo in 138 patients aged 4–30 years. LGS was started at a dose of 10 mg/kg and was titrated over a 7-day period to a maximal dose of 45 mg/kg/d.[e50] Patients randomized to RFN experienced a significantly greater median percent reduction in total seizure frequency and in the frequency of drop attacks, and significantly greater improvement in seizure severity and responder rate for total seizures. Six

patients, all taking RFN, withdrew from the study because of AEs. Common AEs included somnolence and vomiting.

The second study consisted of a multicenter double-blind RCT in 59 patients with LGS (4–30 years old), 29 of whom were randomized to RFN and 30 to placebo.[e51] The median percent change in frequency of tonic–atonic seizures was significantly higher in patients on RFN than placebo as well as that of total seizures. The common AEs associated with RFN included decreased appetite, somnolence, and vomiting. Of note, this study was conducted only in Japanese patients.

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

Recommendations
For LGS, RFN use should be considered established as effective to decrease seizure frequency as add-on therapy for LGS (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 practice guideline, GBP, LTG, OXC, and TPM were found to be effective as add-on therapy in treating TR epilepsy in children. Since then, 4 studies have been published, 2 on LEV and ZNS use in children and 2 on LEV and OXC use in infants and young children.

Levetiracetam
One Class I multicenter double-blind RCT was conducted in 198 children aged 4–16 years, who were randomized to placebo or an initial dose of LEV of 20 mg/kg/d to reach a target dose of 60 mg/kg/d over 6 weeks.[e52] A significantly greater median reduction in seizure frequency per week and > 50% seizure frequency reduction per week were found for LEV than placebo. LEV was associated with more frequent AEs than placebo, including somnolence, accidental injury, vomiting, anorexia, rhinitis, hostility, increased cough, pharyngitis, and nervousness. AE-related withdrawal from the study was higher among children randomized to placebo (9.3%) than to LEV (5.5%).

The second Class I study was a multicenter double-blind RCT in 116 children aged 1 month to < 4 years who were randomized to placebo or LEV at a dose of 40 mg/kg/d (if aged 1 to < 6 months) or 50 mg/kg/d (if aged ≥6 months to < 4 years).[e53] The study included a 48-hour inpatient baseline video electroencephalography and a 5-day inpatient treatment period with one-day up-titration and a 48-hour evaluation with video electroencephalography in the last 2 days. Children randomized to LEV had a significantly greater responder rate in average daily seizure frequency and greater median percent reduction from baseline in the average of daily seizure frequency with LEV. Five children were withdrawn from the study. The most frequently reported AEs related to LEV 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 single (rater)–blind, multicenter, randomized, parallel-group study of 128 children aged 1 month to < 4 years compared the efficacy and tolerability of 2 doses of OXC, 10 mg/kg/d and 60 mg/kg/d, given as add-on therapy in an oral suspension.[e54] The primary outcome was absolute change in the frequency of focal seizures per 24 hours during 3 days of continuous treatment-phase video electroencephalography compared with baseline seizure frequency. Children on the higher OXC dose experienced a significantly greater seizure frequency reduction than those on the low dose and a greater median percent reduction in seizure frequency per 24 hours. Children in the high-dose group also experienced more frequent AEs than those in the low-dose group (31.3% vs 4.7%), which included somnolence, ataxia, and vomiting. Five patients, 2 in the low-dose group and 3 in the high-dose group, discontinued because of AEs.

Conclusion

OXC is probably effective as add-on therapy in infants and young children with TR focal epilepsy (1 Class I study). Because of the short duration of the study, however, generalizability for long-term use may be limited.

Zonisamide

One Class I double-blind, multicenter, randomized, placebo-controlled trial of 207 children and adolescents aged 6–17 years compared the efficacy and tolerability of ZNS at a dose of 8 mg/kg/d with placebo.[e55] Patients were started on 1 mg/kg/d, with titration over an 8-week period. The primary outcome was the responder rate during a 12-week maintenance period, which was found to be significantly higher for the patients randomized to ZNS. The incidence of AEs did not differ between the 2 groups, including serious AEs (3.7% for ZNS vs 2% for placebo), although AEs leading to withdrawal were higher in the placebo group (3% for ZNS vs 0.9% for placebo). The AEs reported with a higher frequency in the ZNS group included decreased appetite, decreased weight, somnolence, vomiting, and diarrhea.

Conclusions

ZNS is probably effective as add-on therapy for TR focal epilepsy in children and adolescents (1 Class I study). There are no data on the efficacy of CLB, ESL, LCM, PER, PGB, RFN, TGB, or VGB as add-on therapy for the treatment of children or adolescents with TR focal epilepsy.

Recommendations

For add-on therapy for treatment of children and adolescents with 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 to 17 years), and OXC use should be considered to decrease seizure frequency (Level B for ages 1 month to 4 years).

There are no data on the efficacy of CLB, ESL, LCM, PER, PGB, RFN, TGB, or VGB as add-on therapy for the treatment of children or adolescents with TR focal epilepsy (Level U).

Clinical context
A pharmacokinetic: pharmacodynamic analysis performed comparing adults with children receiving approved AEDs showed that, in each case where the serum concentrations were similar, there was similar seizure reduction for the 2 groups. On the basis of these data, the FDA has determined that efficacy of AEDs for focal seizures in adults can be extrapolated downward to children 4 years of age.[e56] However, trials in pediatric populations are very important to establish efficacy in this and in other pediatric-specific epilepsy syndromes, to evaluate efficacy in children younger than 2 years of age, to identify specific safety issues, and to characterize the dosing and pharmacokinetic properties. Further, it is essential to assess safety issues in the entire pediatric population.

For pediatric patients with TR focal epilepsy, are these AEDs effective as monotherapy in reducing seizure frequency?
The 2004 guidelines[e1,e2] did not find any relevant evidence that any of the new AEDs were effective. No new studies were identified.

Recommendation
Data are insufficient regarding the use of newer AEDs as monotherapy in pediatric patients with TR focal epilepsy (Level U).

Clinical context
The studies performed to demonstrate effectiveness of new AEDs in monotherapy in patients with refractory focal seizures are difficult to interpret, because they are driven by FDA requirements to show superiority to placebo, pseudoplacebo, or historical control rather than by clinical questions. Dosages used in the trials are often higher than those that might be used in practice because the goal is to retain as many patients as possible and achieve a significant result. Most important, the goal of these studies is not to determine whether patients improve after they are converted to monotherapy; rather, the goal is to determine whether their condition deteriorates to a lesser degree than that of the comparison group.

Valproate carries significant teratogenic risk of at least 9-10% in a dose-related manner, specifically for midline neuroaxis and penile congenital malformations (site Harden , et al 2009 guideline). Therefore, valproate should not be used in women of child-bearing potential unless other antiseizure medications are not effective, and there should be a detailed discussion with the patient regarding risk versus benefits of taking valproate during child-bearing years.

Notably, a recent FDA strategy allows extrapolation of efficacy across populations; therefore, eslicarbazepine and lacosamide (oral only for pediatric age group) received FDA approval for treatment of focal epilepsy as add-on or monotherapy in persons aged 4 years and older, and perampanel received FDA approval for monotherapy for focal epilepsy.

Have new SAEs been identified in the AEDs evaluated in the 2004 guideline?
The SAEs of the original 8 AEDs have been summarized in the previous guidelines. There are no new reported SAEs associated with these drugs.

RECOMMENDATIONS FOR FUTURE RESEARCH

Add-on trials in patients with refractory partial seizures are the mainstay of new AED approval. These are not ideal trials; they are of short duration, enroll patients that are not representative of those seen in common neurologic practice, and often use titration schedules and doses that are ultimately found to be suboptimal. As a result, this practice guideline can determine that drugs are effective and yet provide few evidence-based data on titration, dosing, optimal serum levels, outcome in patients presenting more typically, and, most important, comparative safety and efficacy between drugs. Regulatory studies must be supplemented with controlled trials that investigate optimal clinical use.[e2]

There is a serious lack of head-to-head trials 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 that are commonly used in clinical practice and use flexible-dosing regimens. Finally, there is a very serious lack of placebo-controlled and head-to-head trials of the newer AEDs in pediatric patients of all ages.

DISCLAIMER

Clinical practice guidelines, practice advisories, systematic reviews and other guidance published by the American Academy of Neurology and its affiliates are assessments of current scientific and clinical information provided as an educational service. The information: 1) should not be considered inclusive of all proper treatments, methods of care, or as a statement of the standard of care; 2) is not continually updated and may not reflect the most recent evidence (new evidence may emerge between the time information is developed and when it is published or read); 3) addresses only the question(s) specifically identified; 4) does not mandate any particular course of medical care; and 5) is not intended to substitute for the independent professional judgment of the treating provider, as the information does not account for individual variation among patients. In all cases, the selected course of action should be considered by the treating provider in the context of treating the individual patient. Use of the information is voluntary. AAN provides this information on an "as is" basis, and makes no warranty, expressed or implied, regarding the information. AAN specifically disclaims any warranties of merchantability or fitness for a particular use or purpose. AAN assumes no responsibility for any injury or damage to persons or property arising out of or related to any use of this information or for any errors or omissions.

CONFLICT OF INTEREST

The American Academy of Neurology (AAN) and the American Epilepsy Society (AES) 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 three AAN committees, three 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 www.aan.com. For complete information on this process, access the 2004 AAN process manual.[e3]

Appendix e-1. AAN GDDI mission

The mission of the GDDI is to develop, disseminate, and implement evidence-based systematic reviews and clinical practice guidelines related to the causation, diagnosis, treatment, and prognosis of neurologic disorders.

The GDDI is committed to using the most rigorous methods available within its budget, in collaboration with other available AAN resources, to most efficiently accomplish this mission.

Appendix e-2. AAN GDDI members 2015–2017

Cynthia Harden, MD (Chair); Steven R. Messé, MD (Co-Vice-Chair); Sonja Potrebic, MD, PhD; (Co-Vice-Chair); Eric J. Ashman, MD; Stephen Ashwal, MD; Brian Callaghan, MD; Jane Chan, MD; Gregory S. Day, MD, MSc; Diane Donley, MD; Richard M. Dubinsky, MD, MPH; Gary S. Gronseth, MD (Senior evidence-based medicine methodology expert); Jeffrey Fletcher, MD; Michael Haboubi, DO; John J. Halperin, MD; Yolanda Holler-Managan, MD; Annette M. Langer-Gould, MD, PhD; Nicole Licking, DO; David Michelson, MD; Pushpa Narayanaswami, MBBS, DM; Maryam Oskoui, MD; Alejandro A. Rabinstein, MD; Alexander Rae-Grant, MD; Kevin Sheth, MD; Kelly Sullivan, PhD; Jacqueline French, MD (Guideline Process Historian)

Appendix e-3. AES committee members

AES Guidelines and Assessment Committee; Approval on Wednesday, September 13, 2017
David Gloss, MD, Chair; Paul Cooper, MD, MA, FRCP; Jacqueline A. French, MD; Tracy A. Glauser, MD; Cynthia L. Harden, MD; Nathalie Jette, MD, FRCPC; Marissa A. Kellogg, MD, MPH; Carrie R. McDonald, PhD; Lilit Mnatsakanyan,MD; Rebecca O'Dwyer Vourganti, MD; Rani Sarkis, MD, MSc; James W. Wheless, MD

AES Council on Clinical Activities; Approval on Wednesday, September 13, 2017
Barbara Dworetzky, MD, Chair; David Gloss, MD; Gabriel U. Martz, MD; David G. Vossler, MD; Timothy E. Welty, MD, MA, PharmD

AES Board of Directors Approval on September 16, 2017
Eli M. Mizrahi, MD, President; Shlomo Shinnar, MD, PhD, 1st Vice President; Page B. Pennell, MD, 2nd Vice President; Michael Privitera, MD, President Emeritus; William Theodore, MD Treasurer; Anne Anderson, MD; Gregory Bergey, MD; Douglas Coulter, PhD; Howard Goodkin, MD, PhD; Robert Hogan, MD; Georgette Smith, PhD, RN, CPNP-PC

Appendix e-4. Search strategy

The original and updated literature searches were performed in an identical manner. The search strategy is available as a data supplement PDF at Neurology.org.

Appendix e-5. AAN rules for classification of evidence for risk of bias

Therapeutic scheme

Class I

A randomized controlled clinical trial of the intervention of interest with masked or objective outcome assessment, in a representative population. Relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences.

The following are also required:

a. concealed allocation

b. primary outcome(s) clearly defined

c. exclusion/inclusion criteria clearly defined

d. adequate accounting for dropouts (with at least 80% of enrolled subjects completing the study) and crossovers with numbers sufficiently low to have minimal potential for bias.

e. For noninferiority or equivalence trials claiming to prove efficacy for one or both drugs, the following are also required*:

1. The authors explicitly state the clinically meaningful difference to be excluded by defining the threshold for equivalence or noninferiority.
2. The standard treatment used in the study is substantially similar to that used in previous studies establishing efficacy of the standard treatment (e.g., for a drug, the mode of administration, dose and dosage adjustments are similar to those previously shown to be effective).
3. The inclusion and exclusion criteria for patient selection and the outcomes of patients on the standard treatment are comparable to those of previous studies establishing efficacy of the standard treatment.
4. The interpretation of the results of the study is based upon a per-protocol analysis that takes into account dropouts or crossovers.

Class II

A randomized, controlled clinical trial of the intervention of interest in a representative population with masked or objective outcome assessment that lacks one criteria a–e above (see Class I) or a prospective matched cohort study with masked or objective outcome assessment in a representative population that meets b–e above (see Class I). Relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences.

Class III

All other controlled trials (including well-defined natural history controls or patients serving as own controls) in a representative population, where outcome is independently assessed, or independently derived by objective outcome measurement.**

Class IV

Studies not meeting Class I, II, or III criteria, including consensus or expert opinion.

* Note that numbers 1–3 in Class Ie are required for Class II in equivalence trials. If any one of the three is missing, the class is automatically downgraded to Class III.

*Objective outcome measurement: an outcome measure that is unlikely to be affected by an observer's (patient, treating physician, investigator) expectation or bias (e.g., blood tests, administrative outcome data).

Appendix e-6. Classification of recommendations

A = Established as effective, ineffective, or harmful (or established as useful/predictive or not useful/predictive) for the given condition in the specified population. (Level A rating requires at least two consistent Class I studies.)*

B = Probably effective, ineffective, or harmful (or probably useful/predictive or not useful/predictive) for the given condition in the specified population. (Level B rating requires at least one Class I study or two consistent Class II studies.)

C = Possibly effective, ineffective, or harmful (or possibly useful/predictive or not useful/predictive) for the given condition in the specified population. (Level C rating requires at least one Class II study or two consistent Class III studies.)

U = Data inadequate or conflicting; given current knowledge, treatment (test, predictor) is unproven.

*In exceptional cases, one convincing Class I study may suffice for an "A" recommendation if 1) all criteria are met, 2) the magnitude of effect is large (relative rate improved outcome > 5 and the lower limit of the confidence interval is > 2).

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