Practice guideline update: Efficacy and tolerability of the new antiepileptic drugs I: Treatment of new-onset 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.

C. Harden receives royalties from UpToDate and Wiley; serves on the speakers bureau for UBC; and has received research support from the National Institute of Neurological Disorders and Stroke (NINDS) of the NIH and the Epilepsy Therapy Project.

B. Bourgeois serves on the data and safety monitoring board for a clinical trial conducted by Pfizer Pharmaceuticals, for which he receives honoraria; and receives royalties for *The Epilepsy Prescriber's Guide to Antiepileptic Drugs*.

J. Bautista serves on the National Quality Forum Neurology Steering Committee and the Neurology Endorsement Maintenance Committee and has received research funding from the NIH and NINDS.

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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D. Hirtz reports no relevant disclosures.

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ABBREVIATIONS

AAN: American Academy of Neurology
ACE: active control equivalence
AE: adverse event
AED: antiepileptic drug
CBZ: carbamazepine
CBZ-CR: controlled-release carbamazepine
CBZ-IR: immediate-release carbamazepine
CLB: clobazam
ESL: eslicarbazepine
ETS: ethosuximide
EZG: ezogabine
FBM: felbamate
GBP: gabapentin
GE: generalized epilepsy
GTC: generalized tonic–clonic
JME: juvenile myoclonic epilepsy
LCM: lacosamide
LEV: levetiracetam
LTG: lamotrigine
OXC: oxcarbazepine
PER: perampanel
PGB: pregabalin
PHT: phenytoin
RCT: randomized controlled trial
RFN: rufinamide
TGB: tiagabine
TPM: topiramate
TR: treatment resistant
VGB: vigabatrin
VPA: valproic acid
VPA-ER: extended-release valproic acid
ZNS: zonisamide

ABSTRACT

Objective: To update the 2004 American Academy of Neurology (AAN) guideline for treating new-onset focal or generalized epilepsy (GE) with second- and third-generation antiepileptic drugs (AEDs).

Methods: The guideline panel used 2004 AAN criteria to systematically reviewed literature published from January 2003 to November 2015 (the previous guideline covered literature from 1987–2003); classify pertinent studies according to the AAN therapeutic scheme; and link recommendations to evidence strength. One question was addressed on the effectiveness and safety of newer AEDs for monotherapy in newly diagnosed epilepsy, and how these compare with those of older AEDs.

Results: Several second-generation AEDs are effective for new-onset focal epilepsy. Data are lacking on efficacy in new-onset generalized tonic–clonic seizures, juvenile myoclonic epilepsy, or juvenile absence epilepsy, and on efficacy of third-generation AEDs in new-onset epilepsy.

Recommendations: Lamotrigine (LTG) should (Level B) and levetiracetam (LEV) and zonisamide (ZNS) may (Level C) be considered for use in decreasing seizure frequency in adults with new-onset focal epilepsy. LTG should (Level B) and gabapentin (GBP) may (Level C) be considered for use in deceasing seizure frequency in patients aged ≥60 years with new-onset focal epilepsy. Unless there are compelling adverse-effect-related concerns, ethosuximide (ETS) or valproic acid (VPA) should be considered for use before LTG to decrease seizure frequency in treating absence seizures in childhood absence epilepsy (Level B). No high-quality studies suggest clobazam, eslicarbazepine, ezogabine, felbamate, GBP, lacosamide, LEV, LTG, oxcarbazepine, perampanel, pregabalin, rufinamide, tiagabine, topiramate, vigabatrin, or ZNS is effective in treating new-onset epilepsy because no high-quality studies exist in adults of various ages. 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

In 2004, the American Academy of Neurology (AAN) and the American Epilepsy Society published the first evidence-based guidelines on use of 7 second-generation antiepileptic drugs (AEDs): gabapentin (GBP), lamotrigine (LTG), levetiracetam (LEV), oxcarbazepine (OXC), tiagabine (TGB), topiramate (TPM), and zonisamide (ZNS).[e1,e2] A guideline on the evidence for the efficacy, safety, and tolerability of felbamate (FBM) in intractable epilepsy was published separately and was last reaffirmed on July 16, 2016.[e3] Principal findings from the 2004 guidelines are summarized in table e-1.

Since the 2004 guideline publications, new studies emerged in the 8 second-generation and 6 newer, or third-generation, AEDs (eslicarbazepine [ESL], ezogabine [EZG], lacosamide [LCM], perampanel [PER], pregabalin [PGB], and rufinamide [RFN]). The US Food and Drug Administration has since approved 2 older AEDs (clobazam [CLB] and vigabatrin [VGB], in use for decades in Canada, Europe, and Latin America), for treating certain types of epileptic disorders in the United States.

This update reviews new evidence for efficacy, safety, and tolerability of CLB, VGB, and the 8 second-generation and 6 third-generation AEDs. The 2004 guidelines examine the mechanisms of action, common and serious adverse events (AEs), and pharmacokinetic properties of the second-generation AEDs.[e1–e3] The following clinical question is addressed in this guideline update: For adults and children with newly diagnosed epilepsy, are CLB, ESL, EZG, FBM, GBP, LCM, LEV, LTG, OXC, PER, PGB, RFN, TGB, TPM, VGB, and ZNS effective individually as monotherapy in newly diagnosed epilepsy, and how does their efficacy and tolerability compare with those of older AEDs?

A companion guideline update[e4] examines the evidence regarding the identified mechanisms of action of the 6 third-generation AEDs, CLB, and VGB; their common and serious AEs; and their clinically relevant pharmacokinetic properties in treatment resistant (TR) epilepsy.

DESCRIPTION OF THE ANALYTIC PROCESS

The 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 AAN 2004 Clinical Practice Guideline Process Manual[e5] was used in the development of this update. New studies were identified through computerized searches of the MEDLINE, EMBASE, Science 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 serious adverse events, 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 be included if important AEs were identified. For each study, the most frequent AEs and the AEs leading to discontinuation from the trial were identified. Recommendations were linked to the strength of the evidence (appendix e-6).

ANALYSIS OF EVIDENCE

The original search identified 1,172 citations. The supplemental search from week 11 of 2008 to the last week of November 2014 yielded an additional 1,216 citations. Of the 2,388 total citations, the articles of 478 met criteria for full review. For the 8 AEDs reviewed in the original guidelines, only studies that resulted in a Level A, B, or C recommendation are discussed here. For third-generation AEDs not included in the 2004 guideline, studies that resulted in a Level U recommendation were also included. All statistical data are presented in table e-2. When the class of evidence in a study was downgraded for reasons other than the criteria in appendix e-5, the cause for this action was included in table e-2.

Since publication of the previous guideline, the AAN has updated its criteria for levels of evidence related to active control equivalence (ACE) trials. Therefore, the ACE trials of 4 AEDs (GBP, LTG, OXC, and TPM) for which a Level A or B recommendation was made in the 2004 guideline were revisited using the new methodology to determine the level of evidence for these AEDs.

For adults and children with newly diagnosed epilepsy, are CLB, ESL, EZG, FBM, GBP, LCM, LEV, LTG, OXC, PER, PGB, RFN, TGB, TPM, VGB, and ZNS effective as monotherapy, and how does their efficacy and tolerability compare with those of older AEDs?

The original practice guidelines included studies that enrolled patients with a mixed group of syndromes (focal epilepsy, generalized tonic–clonic [GTC] seizures associated with generalized epilepsy [GE], and unclassified GTC seizures). With the previous level of evidence criteria, there were 3 Class I LTG studies (2 in patients aged 60 years and older and 1 in patients aged 65 years and older),[e6–e8] 4 Class I OXC studies,[e9–e12] and 2 Class I TPM studies.[e13,e14] Accordingly, these 3 AEDs were considered to be effective as monotherapy in treating adults with new-onset focal and GTC seizures; however, evidence was insufficient to make recommendations for specific syndromes. On the basis of 1 Class I study, GBP was considered to be effective as monotherapy only in the treatment of new-onset focal epilepsy.[e15] With the 2004 criteria, the 3 LTG studies and the 1 GBP study were downgraded from Class I to Class II, and the 2 TPM studies were lowered from Class I to Class III. The 4 OXC studies remain Class I. Thus, GBP and TPM are considered possibly effective (Level C) and LTG probably effective (Level B), and the OXC recommendation level remains unchanged (Level A).

Monotherapy in adults with new-onset epilepsy with focal epilepsy or unclassified tonic–clonic seizures

Since the 2004 guideline publications, 2 Class I, 5 Class II, and 2 Class III studies have been published. One study was conducted in patients aged ≥60 years and one in patients aged ≥65 years.

GBP vs LTG vs carbamazepine

A Class II double-blind randomized study compared the efficacy and tolerability of GBP (≤1,500 mg/d), LTG (≤150 mg/d), and immediate-release carbamazepine (CBZ-IR) (≤600 mg/d), in a tiered titration, in 593 patients aged ≥60 years with newly diagnosed focal epilepsy[e16]; the primary outcome was retention in the trial for 12 months on the basis of seizure recurrence or AEs despite dose adjustments. Drug discontinuation was less frequent among patients randomized to LTG (44.2%) than those randomized to GBP (51%) or CBZ-IR (64.5%) because of better LTG tolerability. All significant differences were related to the occurrence of AEs (12.1% taking LTG, 21.6% taking GBP, and 31% taking CBZ-IR). Pairwise comparisons yielded significant differences in AE occurrence between LTG and CBZ-IR and between LTG and GBP. The most frequently occurring AEs included weight gain and water retention among patients taking GBP compared with patients taking LTG or CBZ a higher occurrence of rash with CBZ than with LTG, and hyponatremia that was more frequent with CBZ than with GBP. The 3 AEDs did not differ with respect to occurrence of neurologic AEs. Of note, the patients included in this study had a high prevalence of head trauma and may not be representative of most elderly patients with focal epilepsy.

LTG vs controlled-release carbamazepine

The differences between LTG and CBZ-IR identified in the study described in the preceding section were not reproduced in a Class I multicenter, double-blind, parallel randomized controlled trial (RCT) in 185 patients aged ≥65 years that compared the efficacy and tolerability of LTG and controlled-release carbamazepine (CBZ-CR) in treating focal epilepsy.[e17] LTG doses could be adjusted from 100 mg/d to a maximum of 500 mg/d and CBZ-CR from 400 mg/d to 2,000 mg/d in the maintenance phase of the trial. Retention in the trial was the primary outcome based on seizure recurrence and AE occurrence. There were no significant differences in the numbers of patients in either treatment arm (73% for LTG and 67% for CBZ-CR), in time to withdrawal for any reason, or in the number of completers who were seizure free in the previous 20 weeks (52% for LTG vs 57% for CBZ-CR). AE occurrence leading to withdrawal was higher for CBZ-CR (14% for LTG vs 25% for CBZ-CR) but did not reach statistical significance (p = 0.078). Among patients on LTG, the most common AEs included dizziness, headache, and fatigue. Rash, headache, dizziness, somnolence, and fatigue were identified more frequently among those on CBZ.

LEV vs CBZ-CR

A Class II multicenter, double-blind, parallel RCT compared the efficacy and tolerability of 1,000 mg/d of LEV and 400 mg/d of CBZ-CR in 579 adults. Eighty percent had ≥2 focal seizures and 20% had unclassified GTC seizures in the preceding 12 months.[e18] Doses could be increased incrementally up to 3,000 mg/d for LEV and up to 1,200 mg/d for CBZ-CR. Seizure-free rates were almost identical for LEV (73%) and CBZ-CR (72.8%) at 6 months and 1 year. Of note, 6-month seizure freedom was achieved at the lowest doses (1,000 mg/d for LEV and 400 mg/d for CBZ-CR) in 80.1% of responder patients on LEV and 85% on CBZ-CR. AE occurrence led 14.4% of patients on LEV and 19.2% on CBZ-CR to withdraw from the trial; this difference did not reach statistical significance. Depression and insomnia occurred significantly more frequently with LEV; back pain and weight gain occurred significantly more frequently with CBZ-CR. Headache, fatigue, somnolence, and dizziness were the most frequent AEs identified with both AEDs. The relatively low number of patients with unclassified GTC seizures makes it difficult to establish the efficacy of LEV in this type of seizure from this study.

ZNS vs CBZ-CR

A Class II multicenter, double-blind, parallel RCT compared ZNS and CBZ-CR in 583 adults, 74% of whom had newly diagnosed focal epilepsy and 26% of whom had at least 2 GTC seizures without a clear focal onset.[e19] Primary outcome was the percentage of patients who achieved seizure freedom for 26 weeks. Doses could be increased incrementally from 300 mg/d up to 500 mg/d for ZNS and from 600 mg/d up to 1,200 mg/d for CBZ-CR, according to response and tolerance. Seizure-free rates for 26 weeks were nearly identical for ZNS (79.4%) and CBZ-CR (83.7%). AE occurrence led 11% of patients on ZNS and 12% on CBZ-CR to withdraw from the trial. Decreased appetite and weight loss occurred more frequently with ZNS use and dizziness with CBZ-CR use. Headache, dizziness, and somnolence were the most frequent AEs in both AEDs. As noted in the study comparing LEV and CBZ-CR, the relatively low number of patients with unclassified GTC seizures makes it difficult to establish the efficacy of ZNS in this seizure type from this study.

LTG vs GBP vs TPM vs OXC vs carbamazepine

SANAD (Standard and New Antiepileptic Drugs)-Arm A trial is a Class III randomized unblinded trial, conducted in 1,721 outpatient children and adults with epilepsy in which carbamazepine (CBZ) was "deemed to be the better standard treatment option when compared to valproate."[e20] In this trial, 82.1% had new-onset epilepsy, 15.5% had a seizure disorder that failed to remit with a previous monotherapy regimen (excluding the AEDs studied in this trial), and 2.5% were in remission but relapsed after discontinuing the AED. Focal epilepsy was diagnosed in 89% of patients; 9.5% had unclassified GTC seizures and 1.3% had a GE. Patients were randomized to CBZ (CBZ-IR or CBZ-CR), GBP, LTG, OXC, or TPM. Primary outcomes were time to treatment failure and time to 12-month remission. Clinicians were allowed to choose the starting AED dose, formulation (i.e., immediate release or controlled release), titration rate, and initial maintenance dose, but any further dose changes were made using guidelines. For time to treatment failure, LTG outperformed CBZ, GBP, and TPM and had a nonsignificant advantage over OXC. For time to 12-month remission, CBZ outperformed GBP and had a nonsignificant advantage over LTG, OXC, and TPM. LTG was noninferior to CBZ for 12-month remission at 2 and 4 years (secondary outcomes). AE intolerability leading to discontinuation was less frequent with GBP (15.2%) and LTG (15.9%) than with OXC (23.3%) and TPM (27%). Although the frequency of tiredness and fatigue was comparable across the AEDs, rash was more frequent with CBZ and OXC; weight gain, dizziness, and ataxia were more frequent with GBP; and psychiatric symptoms (in particular anxiety), weight loss, and paresthesia were more frequent with TPM.

VGB vs CBZ-IR

One Class I study[e21] and 1 Class III study [e22] were available for review. The Class I study was a double-blind, multicenter, parallel RCT that compared the safety and efficacy of 600 mg/d of CBZ-IR and 2,000 mg/d of VGB in 459 patients with newly diagnosed focal epilepsy.[e21] After these target doses were achieved, doses could be adjusted for AEs or seizures. The primary outcome was time to withdrawal due to lack of efficacy or AEs; secondary outcomes included time to 6-month seizure remission, time to first seizure after reaching the initial target dose, and AE development. Although there were no differences between the 2 AEDs regarding time to withdrawal due to lack of efficacy, time to 6-month remission was significantly shorter and time

to first seizure was significantly longer for CBZ-IR than for VGB. VGB was more frequently associated with psychiatric symptoms (25% vs 15% for CBZ-IR) and weight gain (11% vs 5%), and rash occurred more frequently with CBZ-IR (10% vs 3%).

The Class III multicenter, randomized, open-label, parallel study compared the safety and efficacy of CBZ-IR monotherapy with VGB monotherapy in 100 patients aged 15–64 years with new-onset epilepsy. Eighty-one had focal epilepsy, 14 had GTC seizures that could not be classified, and 5 had GTC seizures associated with GE.[e22] Fifty-nine patients who had a single epileptic seizure and were not on AEDs were included as a control for safety measures and were assessed with visual evoked potential studies and neuropsychological tests. The primary outcome variable was the proportion of patients remaining on the AED after 12 months of steady-state treatment. A VGB target dose of 50 mg/kg/d was prescribed, and the CBZ-IR dose was titrated to yield serum concentrations of 20–50 μmol/L. At study completion, 60% of patients were considered to have received a successful treatment, with a significantly lower frequency of seizure freedom among patients on VGB (n = 16) than on CBZ-IR (n = 26). Treatment failure was attributed more frequently to lack of efficacy among patients on VGB (n = 13) and to intolerable AEs (n = 12) among patients on CBZ-IR. AEs related to CBZ-IR included serious rash (15% vs 0% in VGB), and VGB was associated with a significantly higher frequency of scintillating visual disturbances (16% vs 0% on CBZ-IR) and myoclonic jerks (14% vs 2% on CBZ-IR). Of consideration, the risk of a serious AE consisting of a retinopathy involving bilateral concentric constriction of the visual field, more often affecting the nasal rather than the temporal visual fields, was recognized 2 years after this study was published.[e23] The visual field data are reviewed in the companion guideline[e4] on TR epilepsy.

This Class II double-blind, randomized, noninferiority study compared the efficacy and tolerability of PGB (n = 330) and LTG (n = 330) in 660 patients with new-onset focal epilepsy.[e24] In the initial 4 weeks, PGB was titrated up to 150 mg/d and LTG up to 100 mg/d in a bid regimen, after which dosage could be increased to a maximal dose of 600 mg/d of PGB and 500 mg of LTG by the 24th week of the 52-week efficacy phase. The primary outcome consisted of the proportion of patients who were seizure free for 6 continuous months during the efficacy phase. Secondary outcomes included withdrawal due to lack of efficacy, time to first seizure, and time to seizure freedom after dose escalation. Of note, 60% of patients on PGB and 55% on LTG had reached 150 mg/d and 100 mg/d, respectively, by the 24th week of the efficacy phase. Seizure freedom was achieved by a significantly higher number of patients on LTG (68%) than patients on PGB (52%), as LTG use saw a comparatively greater reduction in patients experiencing only secondarily GTC seizures. In addition, LTG performed significantly better than PGB in the 3 secondary variables (see table e-2). With respect to AEs, weight gain was more frequent among patients on PGB (6% vs 2%). Other frequent AEs did not differ in their frequency between the 2 AEDs and included headaches, dizziness, somnolence, and fatigue. In addition, the 2 AEDs differed only slightly in the frequency of withdrawal because of AEs (8% of those taking PGB vs 7% of those taking LTG).

TPM vs phenytoin

One Class II multicenter, double-blind, parallel RCT assessed TPM without titration as an alternative to a loading dose of phenytoin (PHT). The study compared TPM 100 mg/d (as of day 1) and PHT (started with a rapid loading dose of 1,000 mg on day 1 followed by 300 mg/d

maintenance dosing) for the prevention of seizure recurrence over a 28-day period in 259 patients aged 12–65 years with either new-onset (36.7%) or relapsed epilepsy.[e25] Patients had to have experienced 1 to 20 unprovoked focal seizures with altered awareness or GTC seizures resulting from either focal or GE, or both of these conditions, within the previous 3 months. Exposure to an AED within 30 days of randomization led to exclusion from the study. The primary endpoint was time to a recurrence of a first focal seizure with altered awareness or GTC seizure (or both) by study day 28, which occurred in 18.9% of patients on TPM and 9.7% on PHT. Neither noninferiority of TPM to PHT nor superiority of PHT could be established in this study, as a higher percentage of patients on PHT discontinued the drug because of AEs (13.4% vs 6.8% on TPM). The most frequent AEs included dizziness and somnolence. A higher incidence of rash leading to discontinuation occurred in patients on PHT (7.9% vs 0.8% for TPM), and paresthesia was more common with TPM (22% vs 3.9% for PHT). Cognitive AEs occurred more frequently among patients on TPM (confusion: 6.1% vs 1.6% on PHT; difficulty with concentration/attention: 6.1% vs 2.4%). Withdrawal because of cognitive AEs occurred in only 1.5% of patients on TPM (vs 0% of those on PHT). It warrants emphasis that the data from this study apply only to efficacy over 28 days and cannot be generalized to long-term treatment.

Conclusions

1. LTG is probably effective in patients aged ≥60 years with new-onset focal epilepsy (1 Class I study, 1 Class II study). In these 2 studies, LTG was better tolerated than CBZ-IR but not CBZ-CR.
2. GBP is possibly as effective and better tolerated than CBZ-IR in patients aged ≥60 years with new-onset focal epilepsy (1 Class II study).
3. LEV is possibly as effective as CBZ-CR in patients with new-onset focal epilepsy (1 Class II study). AEs were comparable between the 2 AEDs. Not enough patients experienced unclassified GTC seizures to identify differences between CBZ-CR and LEV.
4. ZNS is possibly as effective as CBZ-CR in patients with new-onset focal epilepsy (1 Class II study). The 2 AEDs had comparable AE frequency. Not enough patients had unclassified GTC seizures to identify differences between CBZ-CR and ZNS.
5. Evidence is insufficient to compare the efficacy of GBP, OXC, and TPM with that of CBZ-IR or CBZ-CR in patients with new-onset or relapsing focal epilepsy or unclassified GTC seizures (1 Class III study).
6. VGB is probably less efficacious than CBZ-IR in new-onset focal epilepsy (a secondary endpoint of 1 Class I study and of 1 Class III study). Not enough patients experienced unclassified GTC seizures to identify differences between VGB and CBZ-IR. In addition, VGB is associated with increased risk of serious AEs.
7. PGB was possibly less effective than LTG at the study doses, but the PGB dose was lower than typically used for patients with epilepsy (1 Class II study). Data from this study and the 3 LTG studies [e6–e8] published in the 2004 guideline suggest that LTG is probably effective in the treatment of new-onset focal epilepsy.
8. It was not possible to determine whether TPM is equivalent to PHT in urgent treatment of new-onset or recurrent focal epilepsy, unclassified GTC seizures, or GE presenting with GTC seizures (1 Class II study).
9. No high-quality studies suggest CLB, ESL, EZG, FBM, GBP, LCM, LEV, LTG, OXC, PER, PGB, RFN, TGB, TPM, VGB, or ZNS is effective in the treatment of new-onset epilepsy.

10. Evidence is insufficient to demonstrate AED efficacy in unclassified GTC seizures (no study had enough patients with this seizure type).

Recommendations

In patients with new-onset focal epilepsy or unclassified GTC seizures, the following recommendations apply:

1. LTG use should be considered to decrease seizure frequency (Level B)
2. LTG use should be considered (Level B) and GBP use may be considered (Level C) to decrease seizure frequency in patients ≥60 years
3. LEV use may be considered to decrease seizure frequency (Level C)
4. ZNS use may be considered to decrease seizure frequency (Level C)
5. VGB use appears to be less efficacious than CBZ-IR use and may not be offered (Level C); furthermore, toxicity profile precludes VGB use as first-line therapy
6. PGB use at a dose of 150 mg/d is possibly less efficacious than LTG use at 100 mg/d (Level C)
7. Evidence is insufficient to consider GBP, OXC, or TPM, instead of CBZ (Level U)
8. Evidence is insufficient to consider TPM instead of PHT in urgent treatment of new-onset or recurrent focal epilepsy, unclassified GTC seizures, or GE presenting with GTC seizures (Level U)
9. Data are lacking to support or refute use of third-generation AEDs, CLB, felbamate, or VGB in treating new-onset epilepsy (Level U)
10. Data are lacking to support or refute use of newer AEDs in treating unclassified GTC seizures (Level U)

Monotherapy in children with new-onset epilepsy with either focal epilepsy or unclassified GTC seizures

High-dose vs low-dose TPM

In 1 Class II study, 151 children and adolescents aged 6–15 years were randomized to receive TPM at a target dose of 50 mg/d or 400 mg/d.[e26] In addition to a history of ≥2 lifetime unprovoked seizures, participants had to have experienced at least 1 focal seizure with loss of awareness or a secondarily GTC seizure or generalized-onset GTC seizure in the 3 months before randomization. Time to first seizure was the primary outcome, and seizure-free rates at 6 months and 1 year were secondary variables. Patients randomized to 50 mg/d were started on 25 mg/d for 15 days, and on day 16 the dose was increased to 50 mg/d in 2 divided doses. The mean final TPM dosage was 1.1 (±0.4) mg/kg/d in this group. Patients randomized to 400 mg/d were started at a 50-mg/d dose, which was then titrated up to 200 mg/d over the following 21 days, to 300 mg/d on day 29, and to 400 mg/d on day 36, on the basis of tolerability. The mean final dose was 8.9 (±3.7) mg/kg/d in this group. Kaplan-Meier survival analyses for time to next seizure favored the 400-mg/d dose, and the probability of seizure freedom was significantly higher among patients randomized to 400 mg/d than to 50 mg/d (90% and 78%, respectively, at 6 months and 85% and 62%, respectively, at 12 months). AEs occurred in 4% of children taking 50 mg/d and in 14% of those taking 400 mg/d. The most frequent AEs included headache, decreased appetite, weight loss, somnolence, dizziness, paresthesia, and problems with concentration or attention (or both).

Conclusions

TPM monotherapy at 400 mg/d is possibly more effective than at 50 mg/d in treating children and adolescents with new-onset focal seizures or generalized-onset GTC seizures (Class II study). The higher dose is associated with more AEs and is not used in these patients in clinical practice. It should be noted that this study was done for regulatory and not clinical purposes and that the doses used are not clinically relevant. Therefore, the data from this study are nonapplicable to clinical practice.

Recommendation

Although the data from this study would suggest that TPM monotherapy is possibly more efficacious at 400 mg/d than at 50 mg/d for treating children and adolescents with new-onset focal epilepsy or generalized-onset GTC seizures (1 Class II study), no recommendations can be made regarding TPM use at the studied doses, particularly in new-onset epilepsy and in pediatric patients.

Monotherapy in adults and children with new-onset GE or unclassified GTC seizures

LTG vs TPM vs VPA

A Class III multicenter, randomized, open-label, parallel study, SANAD-Arm B, was conducted in 716 outpatient children and adults with seizure disorders (of which almost 90% had focal epilepsy) in whom a clinician "regarded valproate the better standard treatment option than carbamazepine."[e27] The clinician chose initial doses and formulations. Patients had to have been diagnosed with new-onset epilepsy (87.7% of patients enrolled), have a seizure disorder failing to remit with a previous monotherapy regimen (excluding the AEDs studied in this trial [8.4%]), or have a seizure disorder that was in remission but relapsed after AED discontinuation (3.9%). GE was diagnosed in 63% of patients and focal epilepsy in 7.3%; 27% had unclassified epilepsy. Patients were randomized to receive LTG, TPM, or VPA; the treating clinician determined the target doses based on everyday practice doses. Primary outcomes were time to treatment failure (defined as AED discontinuation because of seizures or AEs, or both) and time to 1-year remission. VPA outperformed TPM for time to treatment failure but was comparable with LTG. When the analysis was restricted to GE, VPA was superior to LTG and TPM. For time to 1-year remission, VPA was superior to LTG when all patients were included or when analysis was restricted to only those with GE, but VPA did not differ from TPM in either analysis. Weight gain was the most frequent AE leading to treatment failure with VPA, and fatigue and psychiatric and cognitive symptoms were the most common AEs associated with TPM. Rash was the most common AE leading to LTG discontinuation (4%).

Conclusion

Evidence is insufficient to compare efficacy of LTG and TPM with that of VPA in children and adults with new-onset or relapsing GE (1 Class III study).

Monotherapy in adults and adolescents with new-onset focal, GE, or unclassified GTC seizures

LEV vs extended-release VPA or CBZ-CR

KOMET, a Class III multicenter, randomized, open-label, parallel study, compared the effectiveness of LEV with that of extended-release VPA (VPA-ER) or CBZ-CR in 1,688 adolescents (aged ≥ 16 years) receiving outpatient treatment and adults with new-onset epilepsy.[e28] GE was diagnosed in 34.8% of patients and focal epilepsy in 64.7%; 2.1% had an

unclassified epilepsy. The clinician was allowed to choose VPA-ER or CBZ-CR as the better standard treatment option, and patients were then randomized (1:1) to treatment with LEV or 1 of the 2 standard AEDs. Initial target doses were reached over 2 weeks (LEV 1,000 mg/d, VPA-ER 1,000 mg/d, and CBZ-CR 600 mg/d), and with seizure occurrence, the clinician could increase the dose to 3,000 mg/d for LEV, 2,000 mg/d for VPA-ER, and 1,600 mg/d for CBZ-CR. Of the patients randomized to standard AEDs, 65.8% treated with VPA-ER had only GE, and 86.5% treated with CBZ-CR had only focal epilepsy. Primary outcomes were time to treatment failure (defined as AED discontinuation caused by seizures or AEs, or both), and LEV was compared with VPA-ER and with CBZ-CR. Time to treatment withdrawal was similar for LEV and VPA-ER; a nonsignificantly longer time to treatment withdrawal occurred with LEV than with CBZ-CR. The 3 drugs were comparable regarding frequency of drug-related AEs and AEs leading to drug discontinuation. The most frequent AEs were weight gain and tremor with VPA, depression with LEV, and rash with CBZ-CR. Headache, fatigue, and dizziness were equally frequent across these AEDs.

Conclusion.
Evidence is insufficient to compare efficacy of CBZ-CR, LEV, and VPA-ER in adolescents and adults with new-onset GE and focal epilepsy (1 Class III study).

Childhood absence epilepsy
In the 2004 guideline,[e1] LTG was found to be possibly effective for the treatment of childhood absence seizures on the basis of 1 Class II study that included an enriched patient sample (that is, children who had responded to an initial open trial of LTG). Since that publication, a Class I study was published comparing the efficacy, tolerability, and neuropsychological effects of LTG (12 mg/kg/d), ethosuximide (ETS) (60 mg/kg), and VPA (60 mg/kg) in 451 children with newly diagnosed childhood absence epilepsy.[e29] Study outcomes included freedom from treatment failure after 16 weeks (which could be extended to 20 weeks if necessary) and attention disturbances measured with objective tests (e.g., continuous performance test). Children randomized to ETS and VPA had comparable freedom from failure rates (ETS = 53% and VPA = 58%), which were significantly higher than the rates for LTG (29%). Attention disturbances were significantly more common with VPA (49%) than with ETS (33%). These differences in seizure control and cognitive AEs were maintained at a 12-month follow-up evaluation study.[e30]

Conclusion
LTG is probably not as effective as ETS or VPA for treating absence seizures in children with childhood absence epilepsy (1 Class I study). Attention disturbances are more common with VPA use.

Clinical context
ETS use is limited to patients with childhood absence epilepsy without associated GTC seizures.

Recommendation
Unless there are compelling reasons based on the AE profile, ETS or VPA use should be considered before LTG use to decrease seizure frequency in treating absence seizures in childhood absence epilepsy (Level B).

No high-quality studies suggest CLB, ESL, EZG, FBM, GBP, LCM, LEV, LTG, OXC, PER, PGB, RFN, TGB, TPM, VGB, or ZNS is effective in treating new-onset epilepsy.

CLINICAL CONTEXT

Many medication options are available for the treatment of epilepsy. The level of evidence for a specific medication should be considered in conjunction with patient characteristics and preferences as part of an individualized regimen. Furthermore, doses used in AED trials often do not represent those typically prescribed in clinical practice. For example, one of the pediatric trials reviewed in this guideline evaluated the effectiveness of high doses of TPM (400 mg/d) that are not used today in this age group.[e26] By the same token, another study compared the effectiveness of one second-generation AED (LTG) and 1 third-generation AED (PGB) with lower doses than those used in clinical practice,[e24] thus limiting the validity of the findings of such a trial favoring LTG.

The studies examined here on treating new-onset epilepsy were limited to comparisons between first- and second-generation AEDs (and VGB). Therefore, recommendations can be made related only to those medications and cannot be generalized to comparisons involving other AEDs. Furthermore, the majority of the studies included patients with focal epilepsy but also had a small percentage of patients with unclassified GTC seizures. Thus, the data reviewed apply to the treatment of focal epilepsy and limit the ability to make recommendations regarding these drugs for unclassified GTC seizures.

Two studies evaluated the efficacy of TPM,[e27] LTG,[e27] and LEV[e28] in patients with GTC seizures secondary to GE. Unfortunately, both studies were Class III. Accordingly, this guideline cannot make recommendations regarding the second-generation AEDs (LEV, LTG, and TPM) used in the treatment of this type of epilepsy. On the other hand, the Class I study of children with absence epilepsy[e29] suggested that LTG is probably not as effective in this type of epilepsy as the 2004 guideline suggests.

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.

RECOMMENDATIONS FOR FUTURE RESEARCH

In head-to-head studies with patients newly diagnosed, appropriate AED dosing regimens and formulations should be used. Flexible dosing, reflecting clinical practice, should also be used, instead of fixed doses.

As shown by the data reviewed in the 2004 guideline publication and this update, GBP, LEV, LTG, OXC, and ZNS are second-generation AEDs that can be considered for treating new-onset focal epilepsy. The change in ratings of the 2 TPM studies published in the 2004 guideline[e13,e14] from Class I to Class III suggests that TPM may be possibly effective and that its efficacy should be reinvestigated in an RCT with doses that are used in clinical practice.

To date, no data are available on the efficacy and tolerability of TGB or of any of the third-generation AEDs and CLB in treatment of new-onset focal epilepsy. Furthermore, the trial with PGB should be repeated using higher doses to establish whether PGB can be considered efficacious.

Among the second-generation AEDs, OXC is the only one with evidence (from 1 Class I study) suggesting its efficacy in new-onset focal epilepsy.[e12] No studies exist on the efficacy of any of the second-generation AEDs in new-onset GE presenting with GTC seizures in children or in adolescents with juvenile absence epilepsy or juvenile myoclonic epilepsy (JME). Furthermore, there are no data on the efficacy of any of the third-generation AEDs in new-onset epilepsy in children. There is a clear and urgent need for RCTs in pediatric patients with new-onset epilepsy.

Second- and third-generation AEDs, CLB, and VGB should be investigated in the treatment of adults with new-onset GE presenting with GTC seizures or JME, as there are currently no current studies addressing these.

Third-generation AEDs found to be equivalent to LTG or CBZ-CR or VPA (or both CBZ-CR and VPA) for treating new-onset focal and generalized epilepsy, respectively, should undergo head-to-head comparisons with third-generation AEDs in double-blind, controlled, parallel studies to compare their effectiveness. Finally, a diverse set of trials, including observational trials, is needed to understand the advantages of the various AEDs available.

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.[e5]

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*:

i. The authors explicitly state the clinically meaningful difference to be excluded by defining the threshold for equivalence or noninferiority.

ii. 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).

iii. 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.

iv. 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 be 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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