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Practice Guideline Update

Efficacy and Tolerability of the New Antiepileptic Drugs II: Treatment-Resistant Epilepsy

Report by:

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

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Presentation Objectives

- To present evidence on the efficacy and tolerability of the new antiepileptic drugs
- To present practice recommendations for the use of new antiepileptic drugs in treatment-resistant epilepsy

Overview

- Introduction
- Clinical questions
- American Academy of Neurology guideline process
- Methods
- Conclusions
- Practice recommendations

Introduction

In 2004, the American Academy of Neurology (AAN) and the American Epilepsy Society published a guideline on felbamate[1] and another guideline on 8 second-generation antiepileptic drugs (AEDs).[2] Since the 2004 publications, the US Food and Drug Administration (FDA) approved 6 new third-generation AEDs and 2 older AEDs.

This update reviews new evidence for efficacy of these AEDs in managing treatment-resistant focal epilepsies and generalized epilepsies (GEs) in children and adults.

Introduction (*continued*)

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

Clinical Questions

This practice guideline addresses the following clinical questions:

1. For adult patients with treatment-resistant (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 generalized epilepsy, are these AEDs effective as adjunctive therapy in reducing seizure frequency (compared with no adjunctive therapy)?
4. For adult and pediatric patients with Lennox-Gastaut syndrome, are these AEDs effective as adjunctive therapy in reducing seizure frequency (compared with no adjunctive therapy)?

Clinical Questions

This practice guideline addresses the following clinical questions:

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 serious adverse events been identified in the AEDs evaluated in the 2004 guideline?

AAN Guideline Process*

- Clinical Questions

- Evidence

- Conclusions

- Recommendations

*Guideline developed using the 2004 *AAN Clinical Practice Guideline Process Manual*.

Literature Search/Review

Rigorous, Comprehensive, Transparent

2,388 abstracts

42 rated articles

MEDLINE, Embase, Scientific Citation Index (using Web of Science), and Cochrane databases were searched from January 2004 to March 2009. An updated search was conducted to include studies published to November 2015. For clobazam and vigabatrin, a search was conducted from 1980 to 2014.

Inclusion criteria:

- Controlled trials
- Observational studies
- Cohort studies
- Open-label studies

Exclusion criteria:

- Studies not published in English
- Studies of fewer than 20 patients except for studies relating to serious adverse events, for which case reports and case series of fewer than 20 patients were accepted.

AAN Classification of Evidence (2004)
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*:

*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.

Class I (continued)

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.

AAN Classification of Evidence (2004)
Therapeutic Scheme

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 (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.*

*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).

AAN Classification of Evidence (2004)
Therapeutic Scheme

Class IV

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

Drug Updates

- 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.
- Production of the drug ezogabine has been discontinued by the manufacturer, and it is no longer available.

Clinical Question 1

For adult patients with treatment-resistant focal epilepsy, are these antiepileptic drugs effective as adjunctive therapy in reducing seizure frequency (compared with no adjunctive therapy)?

Analysis of Evidence (Question 1)

Pregabalin

Immediate-release pregabalin is effective as add-on therapy for treatment-resistant adult focal epilepsy (2 Class I studies). Efficacy and adverse events increased with higher doses. Controlled-release pregabalin is probably not effective (1 Class I study).

Clinical context:

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

Analysis of Evidence (Question 1)

Lacosamide

Lacosamide is probably effective in treatment-resistant adult focal epilepsy (1 Class I study).

Clinical context:

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

Analysis of Evidence (Question 1)

Rufinamide

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

Analysis of Evidence (Question 1)

Ezogabine

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

Clinical context:

In April 2013, the Food and Drug Administration issued a warning that ezogabine can cause blue skin discoloration and retina pigment changes, and recommended that any patient taking ezogabine have baseline and periodic eye examinations. Ezogabine production was discontinued in June 2017.

Analysis of Evidence (Question 1)

Vigabatrin

Vigabatrin is effective as add-on therapy in treatment-resistant adult focal epilepsy (2 Class I studies).

Clinical context:

Benefits of vigabatrin should be weighed against the risks, particularly risk of irreversible retinopathy.

Analysis of Evidence (Question 1)

Clobazam

Clobazam is possibly effective as add-on therapy for treatment-resistant adult 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).

Analysis of Evidence (Question 1)

Perampanel

Perampanel is established as effective as add-on therapy in treatment-resistant adult focal epilepsy (3 Class I studies).

Clinical context:

Patients should be monitored closely for the occurrence of psychiatric adverse events, in particular irritability and aggressive behavior.

Analysis of Evidence (Question 1)

Eslicarbazepine

Eslicarbazepine doses of 800 and 1,200 mg/d are probably effective in treatment-resistant adult focal epilepsy (1 Class I study).

Clinical context:

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

Analysis of Evidence (Question 1)

Extended-release oxcarbazepine

Extended-release oxcarbazepine 2,400 mg/d is possibly effective for treating TRAFE (1 Class II study).

Analysis of Evidence (Question 1)

Extended-release topiramate

Extended-release topiramate is probably effective as add-on therapy for treatment-resistant adult focal epilepsy (1 Class I study).

Clinical Question 2

For adult patients with treatment-resistant focal epilepsy, are these antiepileptic drugs effective in reducing seizure frequency when used as monotherapy?

Analysis of Evidence (Question 2)

Eslicarbazepine is possibly effective as monotherapy for treatment-resistant adult focal epilepsy (2 Class III studies). Evidence is insufficient to determine the efficacy of lacosamide, extended-release levetiracetam, or pregabalin as monotherapy for treatment-resistant adult focal epilepsy (1 Class III study per drug). No new Class I, II, or III studies have been published on clobazam, ezogabine, gabapentin, perampanel, rufinamide, tiagabine, vigabatrin, or zonisamide.

Clinical Question 3

For adult and pediatric patients with treatment-resistant generalized epilepsy, are these antiepileptic drugs effective in reducing seizure frequency when used as adjunctive therapy (compared with no adjunctive therapy)?

Analysis of Evidence (Question 3)

Lamotrigine

Both extended-release lamotrigine and immediate-release lamotrigine are probably effective as add-on therapy for treatment-resistant generalized tonic-clonic seizures (1 Class I study for extended-release lamotrigine; 2 Class II studies for immediate-release lamotrigine.

Analysis of Evidence (Question 3)

Levetiracetam

Levetiracetam is probably effective as add-on therapy for treatment-resistant generalized epilepsy presenting with generalized tonic-clonic seizures (1 Class I study). The data from these studies could be generalized to all patients with treatment-resistant generalized epilepsy; however, the requirement of at least 3 generalized tonic-clonic seizures during the 8-week baseline phase in the first study pertains to patients with more severe generalized epilepsy.

Clinical context:

Only high levetiracetam doses were used.

Clinical Question 4

For adult and pediatric patients with Lennox-Gastaut syndrome, are these antiepileptic drugs effective as adjunctive therapy in reducing seizure frequency (compared with no adjunctive therapy)?

Analysis of Evidence (Question 4)

Clobazam

Clobazam is probably effective as add-on therapy for Lennox-Gastaut syndrome

(2 Class II studies).

Analysis of Evidence (Question 4)

Rufinamide

Rufinamide is established as effective as add-on therapy for Lennox-Gastaut syndrome

(2 Class I studies).

Clinical Question 5

For pediatric patients with treatment-resistant focal epilepsy, are these antiepileptic drugs effective as adjunctive therapy in reducing seizure frequency (compared with no adjunctive therapy)?

Analysis of Evidence (Question 5)

Levetiracetam

Levetiracetam is probably effective as add-on therapy for treatment-resistant focal epilepsy in children and adolescents (1 Class I study). Moreover, levetiracetam is probably effective as add-on therapy in treatment-resistant focal epilepsy in infants and children aged <4 years (1 Class I study).

Analysis of Evidence (Question 5)

Oxcarbazepine

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

Analysis of Evidence (Question 5)

Zonisamide

Zonisamide is probably effective as add-on for treatment-resistant focal epilepsy in children and adolescents (1 Class I study). Data are unavailable on the efficacy of clobazam, eslicarbazepine, lacosamide, perampanel, pregabalin, rufinamide, tiagabine, or vigabatrin as add-on therapy for this group.

Clinical Question 6

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

Analysis of Evidence (Question 6)

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

Clinical Question 7

Have new serious adverse events been identified in the antiepileptic drugs evaluated in the 2004 guideline?

Analysis of Evidence (Question 7)

No new serious adverse events have been identified.

AAN Classification of Recommendations

Level A	• Established as effective, ineffective, or harmful (or established as useful/predictive or not useful/predictive) for the given condition in the specified population. • Requires at least two consistent Class I studies.
Level B	• Probably effective, ineffective, or harmful (or probably useful/predictive or not useful/predictive) for the given condition in the specified population. • Requires at least one Class I study or two consistent Class II studies.
Level C	• Possibly effective, ineffective, or harmful (or possibly useful/predictive or not useful/predictive) for the given condition in the specified population. • Requires at least one Class II study or two consistent Class III studies.
Level U	• Data inadequate or conflicting; given current knowledge, treatment (test, predictor) is unproven. • Studies not meeting criteria for Class I–III.

Recommendations

Level A

- For treatment-resistant adult focal epilepsy, immediate-release pregabalin and perampanel are established as effective to reduce seizure frequency (Level A).
- Vigabatrin and rufinamide should be considered established as effective for decreasing seizure frequency in treatment-resistant adult focal epilepsy but are not first-line agents (retinopathy risk with vigabatrin and modest benefit with rufinamide) (Level A).

Recommendations

Levels A and B

- For Lennox-Gastaut syndrome, rufinamide use should be considered established as effective to decrease seizure frequency as add-on therapy (**Level A**), and clobazam use should be considered (**Level B**).

Recommendations

Level B

- Lacosamide, eslicarbazepine, and extended-release topiramate use should also be considered to decrease seizure frequency in this population [treatment-resistant adult focal epilepsy] (Level B).
- Ezogabine use should be considered to decrease seizure frequency in this population [treatment-resistant adult focal epilepsy] but carries a serious risk of skin and retinal discoloration. (Level B).

Recommendations

Level B
(*continued*)

- For add-on therapy for generalized epilepsy, immediate-release and extended-release lamotrigine use should be considered as add-on therapy to decrease seizure frequency in treating adults with treatment-resistant generalized tonic-clonic seizures secondary to generalized epilepsy. (Level B).
- Levetiracetam use should be considered to decrease seizure frequency as add-on therapy for treatment-resistant generalized tonic-clonic seizures and for treatment-resistant juvenile myoclonic epilepsy. (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.

Recommendations

Level B
(*continued*)

•For add-on therapy for treatment-resistant focal epilepsy, levetiracetam use should be considered to decrease seizure frequency (**Level B for ages 1 month to 16 years**); zonisamide use should be considered to decrease seizure frequency (**Level B for ages 6 years to 17 years**) and oxcarbazepine use should be considered to decrease seizure frequency (**Level B for ages 1 month to 4 years**).

Recommendations

•Clobazam and extended-release oxcarbazepine (OXC) use may be considered to decrease seizure frequency in treatment-resistant adult focal epilepsy. (Level C)

Level C

•Eslicarbazepine use may be considered to decrease seizure frequency as monotherapy for treatment-resistant adult focal epilepsy. (Level C)

Recommendations

Level U

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

Recommendations

Level U
(*continued*)

- Data are unavailable on the efficacy of clobazam, eslicarbazepine, lacosamide, perampanel, pregabalin, rufinamide, tiagabine, or vigabatrin as add-on therapy for the treatment of these children or adolescents [pediatric patients with treatment-resistant focal epilepsy. (Level U).

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

Recommendations for Future Research

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

References

References cited here can be found in the complete guideline, an online data supplement to the summary article. To locate these materials, please visit AAN.com/guidelines.

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Questions?