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Practice Guideline Update

Efficacy and Tolerability of the New Antiepileptic Drugs I: Treatment of New-Onset 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 the treatment of new-onset epilepsy

Overview

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

Introduction

- In 2004, the American Academy of Neurology and the American Epilepsy Society published the first evidence-based guidelines on use of 7 second-generation antiepileptic drugs (AEDs) [e1,e2] :

    1. gabapentin
    2. lamotrigine
    3. levetiracetam
    4. oxcarbazepine
    5. tiagabine
    6. topiramate
    7. zonisamide

- A guideline on the evidence for the efficacy, safety, and tolerability of felbamate in intractable epilepsy was published separately and was last reaffirmed on July 16, 2016.[e3]

Introduction (*continued*)

- Since the 2004 guideline publications, new studies emerged in the 8 second-generation and 6 newer, or third-generation, AEDs:
    1. eslicarbazepine
    2. ezogabine
    3. lacosamide
    4. perampanel
    5. pregabalin
    6. rufinamide
- The US Food and Drug Administration has since approved 2 older AEDs (clobazam and vigabatrin, in use for decades in Canada, Europe, and Latin America), for treating certain types of epileptic disorders in the United States.

Introduction (*continued*)

- This update reviews new evidence for efficacy, safety, and tolerability of clobazam, vigabatrin, and the 8 second-generation and 6 third-generation AEDs.
- A companion guideline update[e4] examines the evidence regarding the identified mechanisms of action of the 6 third-generation AEDs, clobazam, and vigabatrin; their common and serious AEs; and their clinically relevant pharmacokinetic properties in treatment resistant epilepsy.

Clinical Question

This practice guideline addresses the following clinical question:

For adults and children with newly diagnosed epilepsy, are clobazam, eslicarbazepine, ezogabine, felbamate, gabapentin, lacosamide, levetiracetam, lamotrigine, oxcarbazepine, perampanel, pregabalin, rufinamide, tiagabine, topiramate, vigabatrin, and zonisamide effective individually as monotherapy in newly diagnosed epilepsy, and how does their efficacy and tolerability compare with those of older AEDs?

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

478 rated articles

Two databases (MEDLINE and Embase) were searched from January 2004 to March 2009. An updated search was conducted to include studies published to November 2015.

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

For adults and children with newly diagnosed epilepsy, are clobazam, eslicarbazepine, ezogabine, felbamate, gabapentin, lacosamide, levetiracetam, lamotrigine, oxcarbazepine, perampanel, pregabalin, rufinamide, tiagabine, topiramate, vigabatrin, and zonisamide effective individually as monotherapy in newly diagnosed epilepsy, and how does their efficacy and tolerability compare with those of older AEDs?

Analysis of Evidence

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

1. Lamotrigine 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, lamotrigine was better tolerated than immediate-release carbamazepine but not controlled-release carbamazepine.
2. Gabapentin is possibly as effective and better tolerated than immediate-release carbamazepine in patients aged ≥60 years with new-onset focal epilepsy(1 Class II study).
3. Levetiracetam is possibly as effective as immediate-release carbamazepine in patients with new-onset focal epilepsy (1 Class II study). Adverse events were comparable between the 2 antiepileptic drugs. Not enough patients experienced unclassified generalized tonic-clonic seizures to identify differences between controlled-release carbamazepine and levetiracetam.
4. Zonisamide is possibly as effective as controlled-release carbamazepine in patients with new-onset focal epilepsy (1 Class II study). The 2 antiepileptic drugs had comparable adverse event frequency. Not enough patients had unclassified generalized tonic-clonic seizures to identify differences between controlled-release carbamazepine and zonisamide.
5. Evidence is insufficient to compare the efficacy of gabapentin, oxcarbazepine, and topiramate with that of immediate-release carbamazepine or controlled-release carbamazepine in patients with new-onset or relapsing focal epilepsy or unclassified generalized tonic-clonic seizures (1 Class III study).

Analysis of Evidence

Monotherapy in adults with new-onset epilepsy with focal epilepsy or unclassified tonic-clonic seizures (*continued*)

6. Vigabatrin is probably less efficacious than immediate-release carbamazepine in new-onset focal epilepsy (a secondary endpoint of 1 Class I study and of 1 Class III study). Not enough patients experienced unclassified generalized tonic-clonic seizures to identify differences between vigabatrin and immediate-release carbamazepine. In addition, vigabatrin is associated with increased risk of serious adverse events.
7. Pregabalin was possibly less effective than lamotrigine at the study doses, but the pregabalin dose was lower than typically used for patients with epilepsy (1 Class II study). Data from this study and the 3 lamotrigine studies[15-17] published in the 2004 guideline suggest that lamotrigine is probably effective in the treatment of new-onset focal epilepsy.
8. It was not possible to determine whether topiramate is equivalent to phenytoin in urgent treatment of new-onset or recurrent focal epilepsy, unclassified generalized tonic-clonic seizures, or generalized epilepsy presenting with generalized tonic-clonic seizures (1 Class II study).
9. No high-quality studies suggest clobazam, eslicarbazepine, ezogabine, felbamate, gabapentin, lacosamide, levetiracetam, lamotrigine, oxcarbazepine, perampanel, pregabalin, rufinamide, tiagabine, topiramate, vigabatrin, or zonisamide is effective in the treatment of new-onset epilepsy.
10. Evidence is insufficient to demonstrate antiepileptic drug efficacy in unclassified generalized tonic-clonic seizures (no study had enough patients with this seizure type).

Analysis of Evidence

Monotherapy in children with new-onset epilepsy with either focal epilepsy or unclassified generalized tonic-clonic seizures

Topiramate 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 generalized tonic-clonic seizures (1 Class II study). The higher dose is associated with more adverse events and is not used in these patients in clinical practice. Of note, this study was done for regulatory and not clinical purposes, and the doses used are not clinically relevant. Therefore, the study data are nonapplicable to clinical practice.

Analysis of Evidence

Monotherapy in adults and children with new-onset generalized epilepsy or unclassified generalized tonic-clonic seizures

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

Analysis of Evidence

Monotherapy in adults and adolescents with new-onset focal, generalized epilepsy, or unclassified generalized tonic-clonic seizures

Evidence is insufficient to compare efficacy of controlled-release carbamazepine, levetiracetam, and extended-release valproate in adolescents and adults with new-onset generalized epilepsy and focal epilepsy (1 Class III study).

Analysis of Evidence

Childhood absence epilepsy

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

Clinical context:

Ethosuximide use is limited to patients with childhood absence epilepsy without associated generalized tonic-clonic seizures.

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 B

- In patients with new-onset focal epilepsy or unclassified generalized tonic-clonic seizures, lamotrigine use should be considered to decrease seizure frequency (Level B).
- Unless there are compelling reasons based on adverse events profile, ethosuximide or valproate use should be considered before lamotrigine use to decrease seizure frequency in treating absence seizures in childhood absence epilepsy (Level B).

Recommendations

Levels B and C

- In patients with new-onset focal epilepsy or unclassified generalized tonic-clonic seizures, lamotrigine use should be considered (**Level B**) and gabapentin use may be considered (**Level C**) to decrease seizure frequency in patients aged ≥60 years.

Recommendations

Level C

focal epilepsy or unclassified generalized tonic-clonic seizures, vigabatrin use appears to be less efficacious than immediate-release carbamazepine use and may not be offered (Level C); furthermore, toxicity profile precludes vigabatrin use as first-line therapy

Recommendations

Level U

- In patients with new-onset focal epilepsy or unclassified generalized tonic-clonic seizures, evidence is insufficient to consider gabapentin, oxcarbazepine, or topiramate instead of carbamazepine (Level U)
- In patients with new-onset focal epilepsy or unclassified generalized tonic-clonic seizures, evidence is insufficient to consider topiramate instead of phenytoin in urgent treatment of new-onset or recurrent focal epilepsy, unclassified generalized tonic-clonic seizures, or generalized epilepsy presenting with generalized tonic-clonic seizures (Level U)
- In patients with new-onset focal epilepsy or unclassified generalized tonic-clonic seizures, data are lacking to support or refute use of third-generation antiepileptic drugs, clobazam, felbamate, or vigabatrin in treating new-onset epilepsy (Level U)
- In patients with new-onset focal epilepsy or unclassified generalized tonic-clonic seizures, data are lacking to support or refute use of newer antiepileptic drugs in treating unclassified generalized tonic-clonic seizures (Level U)

Clinical Context

The studies examined here on treating new-onset epilepsy were limited to comparisons between first- and second-generation antiepileptic drugs (and vigabatrin). Therefore, recommendations can be made related only to those medications and cannot be generalized to comparisons involving other antiepileptic drugs. The data reviewed apply to treatment of focal epilepsy and limit the ability to make recommendations regarding these drugs for unclassified generalized tonic-clonic seizures.

Clinical Context (*continued*)

The single study wherein the majority of patients had generalized tonic-clonic seizures secondary to generalized epilepsy was Class III, so no recommendations can be made regarding the second-generation antiepileptic drugs (lamotrigine, topiramate) used in treating this epilepsy type. The Class I study of children with absence epilepsy suggested that lamotrigine is probably not as effective in this epilepsy type as the 2004 guideline suggests.

A recent Food and Drug Administration strategy allows extrapolation of efficacy across populations and granted approval of eslicarbazepine and lacosamide (oral only for pediatric age group) as add-on or monotherapy for focal epilepsy in persons ≥4 years old and perampanel as monotherapy for focal epilepsy.

Recommendations for Future Research

Gabapentin, levetiracetam, lamotrigine, oxcarbazepine, and zonisamide are second-generation antiepileptic drugs that can be considered for new-onset focal epilepsy. Change from Class I to Class III of 2 topiramate studies reviewed in the 2004 guideline[23,24] suggests that topiramate may be possibly effective and its efficacy should be reinvestigated in a randomized controlled trial with doses commonly used in clinical practice.

No data are available on efficacy and tolerability of tiagabine or any third-generation antiepileptic drugs and clobazam in treating new-onset focal epilepsy. The trial with pregabalin should be repeated using higher doses to determine whether pregabalin can be considered efficacious.

Recommendations for Future Research (*continued*)

Among second-generation antiepileptic drugs, only oxcarbazepine has evidence from a Class I study suggesting efficacy in new-onset focal epilepsy.[25] No studies exist on efficacy of second-generation antiepileptic drugs in new-onset generalized epilepsy with generalized tonic-clonic seizures in children or adolescents with juvenile absence epilepsy or juvenile myoclonic epilepsy. Data are unavailable about efficacy of third-generation antiepileptic drugs in new-onset epilepsy in children. The need is clear for randomized controlled trials in pediatric patients with new-onset epilepsy.

No data exist on use of second- and third-generation antiepileptic drugs, clobazam, or vigabatrin in treating adults with new-onset generalized epilepsy with generalized tonic-clonic seizures or in juvenile myoclonic epilepsy. Such studies should be included in future research.

Third-generation antiepileptic drugs found equivalent to lamotrigine or to controlled-release carbamazepine or valproate (or both controlled-release carbamazepine and valproate) for treating new-onset focal epilepsy and generalized epilepsy, respectively, should undergo head-to-head comparisons with third-generation antiepileptic drugs in double-blind, controlled, parallel studies for efficacy.

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?