

# Evidence-based guideline: Antiepileptic drug selection for people with HIV/AIDS

Report of the Quality Standards Subcommittee of the American Academy of Neurology and the Ad Hoc Task Force of the Commission on Therapeutic Strategies of the International League Against Epilepsy



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## ABSTRACT

**Objective:** To develop guidelines for selection of antiepileptic drugs (AEDs) among people with HIV/AIDS.

**Methods:** The literature was systematically reviewed to assess the global burden of relevant comorbid entities, to determine the number of patients who potentially utilize AEDs and antiretroviral agents (ARVs), and to address AED-ARV interactions.

**Results and Recommendations:** AED-ARV administration may be indicated in up to 55% of people taking ARVs. Patients receiving phenytoin may require a lopinavir/ritonavir dosage increase of ~50% to maintain unchanged serum concentrations (Level C). Patients receiving valproic acid may require a zidovudine dosage reduction to maintain unchanged serum zidovudine concentrations (Level C). Coadministration of valproic acid and efavirenz may not require efavirenz dosage adjustment (Level C). Patients receiving ritonavir/atazanavir may require a lamotrigine dosage increase of ~50% to maintain unchanged lamotrigine serum concentrations (Level C). Coadministration of raltegravir/atazanavir and lamotrigine may not require lamotrigine dosage adjustment (Level C). Coadministration of raltegravir and midazolam may not require midazolam dosage adjustment (Level C). Patients may be counseled that it is unclear whether dosage adjustment is necessary when other AEDs and ARVs are combined (Level U). It may be important to avoid enzyme-inducing AEDs in people on ARV regimens that include protease inhibitors or nonnucleoside reverse transcriptase inhibitors, as pharmacokinetic interactions may result in virologic failure, which has clinical implications for disease progression and development of ARV resistance. If such regimens are required for seizure control, patients may be monitored through pharmacokinetic assessments to ensure efficacy of the ARV regimen (Level C). *Neurology*® 2012;78:139-145

## GLOSSARY

**AED** = antiepileptic drug; **ARV** = antiretroviral agent; **AUC** = area under the serum concentration-time curve; **CI** = confidence interval; **EI** = enzyme-inducing; **NNRTI** = nonnucleotide reverse transcriptase inhibitor; **PI** = protease inhibitor; **VL** = viral load.

No formal antiepileptic drug (AED) treatment guidelines currently exist for individuals with HIV/AIDS. Seizure disorders are common in individuals infected with HIV, with a reported incidence as high as 11%; provoked seizures resulting from CNS opportunistic infections may also require AED treat-

ment.<sup>1-3</sup> HIV/AIDS, especially prevalent in sub-Saharan Africa, is becoming a chronic condition as antiretroviral (ARV) therapies become increasingly available.<sup>4</sup> The indications for AEDs have expanded to include neurologic conditions other than epilepsy (e.g., painful peripheral neuropathy) and psychiatric

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CME



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Appendices e-1–e-6, tables e-1–e-4, and References e1–e18 are available on the *Neurology*® Web site at [www.neurology.org](http://www.neurology.org).

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conditions. Thus, worldwide the concurrent use of AEDs and ARVs is substantial.

Potential interactions between ARVs and AEDs are complex and extensive. Potential interactions of greatest concern relate to the P450 system enzyme induction effects of several older-generation AEDs (e.g., phenobarbital, carbamazepine, phenytoin) which might be expected to lower the effective dose of nonnucleotide reverse transcriptase inhibitors (NNRTIs) and protease inhibitors (PIs), which are also metabolized by the P450 system. But several additional potential mechanisms of interaction and the impact of ARVs on AEDs also warrant consideration. Effective HIV care requires lifelong treatment using regimens typically comprising at least 3 drugs.<sup>5</sup> Many patients with HIV also require treatment for tuberculosis, which also includes use of enzyme-inducing medications.<sup>6–8</sup> Specific guidelines for treating tuberculosis in the setting of HIV infection have been developed,<sup>9</sup> yet none currently exists for AED-ARV therapy.

AED-ARV interactions that raise blood levels of drugs in either class may increase toxicity risk. Use of ARVs that reduce AED levels could lead to loss of therapeutic AED effects, including seizure control. Use of AEDs that decrease ARV levels (e.g., the enzyme-inducing AEDs [EI-AEDs] phenytoin, phenobarbital, and carbamazepine) may lead to virologic failure, resulting in immunologic decline, clinical disease progression, and development of ARV resistance. Because first-line AED availability in most low- and middle-income countries is limited to phenobarbital, carbamazepine, and phenytoin, and ARV regimen options may also be limited, there is substantial risk for occurrence of clinically important drug interactions.<sup>10,11</sup>

The panel asked the following questions: In people treated with ARVs for HIV/AIDS who also have conditions requiring AED use, does concurrent treatment with AEDs and ARVs lead to drug interactions? If so, are these interactions clinically meaningful? The panel also performed a systematic literature review to estimate the worldwide prevalence of potential co-usage of AEDs and ARVs.

## DESCRIPTION OF THE ANALYTIC PROCESS

**Panel selection.** Given the topic's global relevance, the AAN Quality Standards Subcommittee formed a joint panel with the International League Against Epilepsy via the World Health Organization (WHO). The AAN guideline development processes are consistent with those required by WHO.<sup>12</sup>

**Literature search.** To estimate the worldwide prevalence of potential co-usage of AEDs and ARVs, a literature search (1950 to April 2008, updated 2010)

without language restrictions was conducted using MEDLINE, Cochrane Database, Web of Science, and EMBASE and the following strategy: [prevalence or incidence or epidemiology or comorbid] and [HIV or AIDS] and [neuropathy or seizure or epilepsy]. Given the prevalence of HIV-associated neuropathies in low-income countries and use of AEDs to treat neuropathic pain, we included neuropathy in the search. Because of the dearth of data and the potential clinical value of this information regarding specific AED-ARV combinations, details from case reports and uncontrolled series are provided in the evidence and summary tables.

To determine potential drug–drug interactions between AEDs and ARVs, a comprehensive list of AEDs and ARVs was developed (see table e-1 on the *Neurology*<sup>®</sup> Web site at [www.neurology.org](http://www.neurology.org); note that investigational drugs as of April 2008 were not included). Using this list, the panel performed the following search (1950–2010): drug interaction and [antiepileptic or anticonvulsant or AED or {AED from table e-1}] and [antiretroviral or ARV or ART or {ARV from table e-1}]. The authors' literature files were also hand-searched for potentially relevant articles.

**Literature review.** The broad search yielded 4,480 articles with potential data (1,146 on co-usage of AEDs and ARVs; 3,334 on AED-ARV drug–drug interactions). At least 2 panelists reviewed the resulting articles' titles and abstracts. Additional publications identified during review of selected articles were also obtained. The full article of any abstract deemed relevant was reviewed. At least 2 panelists independently reviewed 68 full articles. Of these, 42 articles were used for data abstraction using the elements listed below for each question. Where data abstraction findings from the 2 panel reviewers differed, a third panelist reviewed the primary source. Data are presented in tables e-2 and e-3. The original and updated search strategies are provided in appendices e-1 and e-2.

## Findings in the systematic review of co-usage of AEDs and ARVs.

Three Class III studies (n = 434, 100, 550) suggest that 2.6%–6.1% of people with HIV will experience a new-onset seizure, with most of these receiving AED treatment, at least initially.<sup>1,2,13,14</sup> Three Class III studies (n = 255, 101, 272) indicate that peripheral neuropathy symptoms occur in 6.7%–52.5% of individuals infected with HIV who have not yet initiated ARV therapy, with the highest rates in advanced HIV and in low- and middle-income countries where dietary deficiencies may contribute to peripheral neuropathy development.<sup>15–18</sup> Two Class III studies (n = 173, 272) indicate that 17%–55% of people without peripheral neuropathy symptoms at ARV initiation will subse-

quently develop such symptoms.<sup>15–17</sup> In an analysis of a US-based cohort with HIV infection (Class II study, n = 1,539), 57% had at least one sign of peripheral neuropathy (abnormal vibratory sensation in the feet or reduced ankle tendon reflexes) on neurologic examination.<sup>19</sup> Among those with peripheral neuropathy, 61% had symptoms, including paresthesias or pain.

**ANALYSIS OF THE EVIDENCE Does concurrent treatment with AEDs and ARVs lead to drug interactions? If so, are these interactions clinically meaningful?** To be included in the analysis, articles had to report human in vivo data and at least one outcome measure, either pharmacokinetic or pharmacodynamic, during coadministration of AEDs and ARVs in comparison with measures during intake of either AEDs or ARVs. For the purpose of characterizing a pharmacokinetic drug interaction, patients with the disease of interest and healthy volunteers were considered to be potentially representative populations. We considered pharmacokinetic crossover studies as equivalent to a prospective matched cohort with an objective outcome (serum concentration), thus meeting criteria for Class II.

Thirty-one articles were identified. Five were rated Class II,<sup>20–24</sup> and 8 were rated Class III.<sup>20,25–38</sup> Two additional articles described data in multiple cohorts, of which one cohort in each article produced Class II evidence and the others Class III.<sup>29,39</sup> Class IV studies are not discussed further (table e-3 presents study details).

**Clinical significance of serum HIV viral load.** We selected the impact of EI-AEDs on serum HIV viral load (VL) in patients treated with ARVs as a clinically important parameter of HIV treatment outcome, because of the abundance of supporting data. The inability to maintain virologic suppression during ARV therapy results in immunologic failure as measured by CD4+ T-cell decline and in clinical HIV disease progression, manifesting as susceptibility to opportunistic infections.<sup>40,e1–e3</sup> Patients with subtherapeutic ARV levels have decreased virologic suppression rates as compared with those with levels in the therapeutic range.<sup>e4</sup> Lack of virologic suppression also leads to development of ARV resistance, limiting the number of potentially efficacious ARVs available for treatment.<sup>e5,e6</sup> Additionally, potential person-to-person transmission of drug-resistant virus has significant public health implications.

**What is the evidence for an interaction between AEDs and PI ARVs? Phenytoin: impact on lopinavir/ritonavir.** A study of 12 healthy volunteers found that phenytoin (300 mg/day for 10 days) reduced mean steady-state area under the serum concentration-time curve

(AUC) of lopinavir and ritonavir by 33% (90% confidence interval [CI] 15% to 47%) and 28% (90% CI 3% to 46%), respectively, as compared with the pre-phenytoin period (Class II).<sup>3</sup>

**Stiripentol: impact on saquinavir.** A randomized, placebo-controlled, crossover study in healthy subjects assessed effects of stiripentol 2,000 mg/day for 8 days on the pharmacokinetics of a single 400-mg dose of saquinavir.<sup>2</sup> Mean saquinavir AUC and maximum plasma concentration ( $C_{max}$ ) were comparable in the stiripentol and the placebo periods, but variability was large, and appropriate sample size to determine equivalence was not calculated in advance (Class III).

**Valproic acid: impact on lopinavir, atazanavir, and ritonavir.** A Class III study in 11 HIV-positive subjects (8 evaluable) taking lopinavir/ritonavir 400/100 found that lopinavir AUC increased on average by 38% (90% CI –2% to 94%) after administration of valproic acid 500 mg/day for 7 days.<sup>29</sup> A Class III study of HIV-positive subjects showed no effect of valproic acid on atazanavir (12 subjects) or ritonavir (9 subjects) levels.<sup>e7</sup>

**Atazanavir and atazanavir/ritonavir: impact on lamotrigine.** A Class II study of 21 healthy volunteers (17 evaluable) assessed the pharmacokinetics of single 100-mg doses of lamotrigine without comedication (day 1) and during coadministration of atazanavir (400 mg/day from day 8 to day 17, with lamotrigine given on day 13) and atazanavir/ritonavir (300/100 mg/day from day 18 to day 32, with lamotrigine given on day 27).<sup>20</sup> Lamotrigine treatment alone was bioequivalent to lamotrigine plus atazanavir, whereas atazanavir/ritonavir reduced lamotrigine AUC by 32% (90% CI 30% to 35%) and lamotrigine half-life by 27% (90% CI 24% to 30%).

**Lopinavir/ritonavir: impact on lamotrigine.** A Class III study assessed the effect of lopinavir/ritonavir (400/100 mg BID) on serum lamotrigine levels at steady state in 24 healthy volunteers,<sup>38</sup> 18 of whom completed 20 days of treatment. Lamotrigine exposure (AUC) on day 20, after 10 days' cotreatment with lopinavir/ritonavir, was 50% (90% CI 47% to 54%) of the value on day 10 during lamotrigine monotherapy. A doubling of the lamotrigine dose was required to achieve serum lamotrigine levels comparable with those prior to lopinavir/ritonavir treatment. Pharmacokinetic parameters for lopinavir/ritonavir were similar to those for historical controls.

**Lopinavir/ritonavir: impact on phenytoin.** In 8 healthy volunteers, lopinavir/ritonavir (400/100 mg BID for 10 days) reduced mean steady-state exposure (AUC) to phenytoin by 31% (90% CI 16% to 43%) (downgraded to Class III because of dropouts).<sup>39</sup>

**Lopinavir/ritonavir: impact on valproic acid.** Serum valproic acid levels in a cohort of subjects infected



with HIV and not receiving lopinavir/ritonavir did not differ significantly from those in subjects comedicated with lopinavir/ritonavir 400/100 mg twice daily; equivalence criteria were not defined (Class III).<sup>29</sup>

**What is the evidence for interaction between AEDs and integrase inhibitors? Raltegravir: Impact on lamotrigine.** One Class II study of 24 healthy volunteers assessed the pharmacokinetics of a single lamotrigine dose (100 mg) with or without raltegravir coadministration (400 mg BID for 5 days).<sup>21</sup> The 90% confidence limits for the geometric ratio of lamotrigine AUC and peak plasma concentration ( $C_{\max}$ ) in the 2 occasions were within bioequivalence range (0.80–1.25), indicating lack of interaction as assessed by this criterion.

**Raltegravir: impact on midazolam.** A 2-period study assessed the influence of raltegravir (800 mg/day) on the pharmacokinetics of midazolam (single 2-mg oral dose), a marker of CYP3A4 activity (Class II).<sup>22</sup> Midazolam AUC and  $C_{\max}$  in the presence and absence of raltegravir remained within bioequivalence limits, suggesting that raltegravir does not affect CYP3A4 activity.

**What is the evidence for an interaction between AEDs and nucleoside reverse transcriptase inhibitor and NNRTI ARVs? Benzodiazepines: impact on zidovudine.** A Class III study found no significant differences in zidovudine levels between patients on benzodiazepines and those off benzodiazepines; statistical power was low.<sup>e8</sup>

**Carbamazepine: Impact on efavirenz.** In a randomized, open-label, crossover study (Class III due to dropouts), 18 healthy subjects<sup>e9</sup> received efavirenz 600 mg/day on days 1–14; on days 15–35 efavirenz 600 mg/day was coadministered with carbamazepine titrated up to 400 mg/day. In the 14 evaluable subjects, carbamazepine reduced efavirenz AUC by 36% (90% CI 32% to 40%) as compared with efavirenz alone.

**Carbamazepine: impact on nevirapine.** In a Class III pilot study in 4 healthy women,<sup>e10</sup> the mean half-life of nevirapine (single 200-mg dose) was reduced after a single 400-mg dose of carbamazepine (from 52 to 33 hours,  $p = 0.021$ ), which corresponds to a median decrease of 18.8 hours (range 15.6–38). These data are difficult to interpret because of the study's small sample size and single-dose design.

**Phenobarbital: impact on nevirapine.** This same Class III study<sup>e10</sup> in 4 women also found no significant change in mean nevirapine half-life after a single 200-mg dose of phenobarbital.

**Phenytoin: impact on nevirapine.** In the same Class III study conducted in healthy women (discussed above),<sup>e10</sup> the mean nevirapine half-life was reduced after phenytoin treatment 184 mg/day for either 3 days

(from 46 to 27 hours,  $p = 0.021$ ) or 7 days (from 55 to 34 hours,  $p = 0.021$ ).<sup>e10</sup> The median (range) decreases in nevirapine half-life were 19 hours (11.4–25.4) and 16.9 hours (10.9–37.4), respectively. There was no significant change in mean nevirapine half-life after a single 184-mg phenytoin dose. Interpretation of these data is limited by the small sample size, short treatment duration, and low phenytoin dose used.

**Valproic acid: impact on efavirenz.** A Class II study in 11 HIV-positive subjects taking efavirenz 600 mg/day found that efavirenz AUC was not significantly affected (mean change 0%, CI –15% to 17%) after administration of valproic acid 500 mg/day for 7 days.<sup>29</sup>

**Valproic acid: impact on zidovudine.** In a Class II open-label study, 6 patients with HIV received zidovudine 100 mg every 8 hours<sup>23</sup>; valproic acid 250 mg every 8 hours was added on days 6–9. Zidovudine levels were measured on days 5 and 10. Coadministration with valproic acid resulted in mean zidovudine AUC increase from 0.65 to 1.17 mg/h/L ( $p < 0.05$ ).

**Efavirenz: impact on carbamazepine.** In a randomized, open-label, crossover study (Class III due to dropouts), 18 healthy subjects<sup>e9</sup> received carbamazepine titrated to 400 mg daily on days 1–21; on days 22–35 carbamazepine 400 mg/day was coadministered with efavirenz 600 mg/day. In the 12 evaluable subjects, efavirenz decreased carbamazepine AUC by 27% (90% CI 20% to 33%) but did not affect levels of the active metabolite carbamazepine-10,11 epoxide.

**Efavirenz: impact on valproic acid.** Valproic acid levels in a cohort of subjects with HIV not receiving efavirenz did not differ significantly from those measured in subjects comedicated with efavirenz 600 mg/day; equivalence criteria were not defined (Class III).<sup>29</sup>

**Zidovudine: impact on phenytoin.** Another Class III study compared patients with AIDS on zidovudine (prospective study arm) plus phenytoin ( $n = 109$  serum samples from 21 patients) with patients without AIDS (historical controls) on phenytoin ( $n = 1,231$  serum samples from 557 patients).<sup>e11</sup> The most commonly prescribed phenytoin dose was 300 mg/day. Addition of zidovudine did not significantly affect phenytoin concentrations in the study patients when compared with levels in the historical controls ( $8.8 \pm 0.88$  mg/L and  $8.9 \pm 1.2$  mg/L, respectively;  $p = 0.99$ ).

**What is the evidence that AED-ARV interactions are clinically meaningful?** One Class II retrospective cohort study<sup>24</sup> (derived from a database with prospective outcome assessment) used data from the US Military HIV Natural History Study. This study matched patients having episodes of overlap of

EI-AED therapy and PI/NNRTI ARV combination therapy (n = 19 patients, 34 episodes of overlap) with patients having episodes of overlap of newer, non-EI-AEDs and PI/NNRTI ARV combinations (n = 85 patients, 142 episodes of overlap). Evidence of virologic failure, as determined by  $\geq 2$  consecutive VL of  $>400$  copies/mL, was assessed. All patients were taking ARVs for  $>6$  months, with episodes of AED and ARV overlap of  $\geq 28$  days. The EI-AED and non-EI-AED cohorts did not differ in CD4 count at ARV initiation, in prior AIDS-defining events, or in ARV therapy type and duration. Patients on EI-AED+ARV therapy had significantly higher rates of virologic failure (10/16, 63%) as compared with patients on non-EI-AED+ARV therapy (20/75, 27%) for the first ARV+AED period, with an odds ratio of 4.58 (90% CI 1.47 to 14.25,  $p = 0.009$ ).<sup>24</sup>

Additionally, 14 case studies (Class IV) described patients whose AED concentrations changed after ARV therapy was initiated.<sup>25–27,30–33,35,e12–e14</sup> In some cases, this provides some confirmatory patient data supporting the significance of the human volunteer data. In other cases, it provides the only available interaction data. Table e-3 presents details regarding these data.

**CONCLUSIONS** Phenytoin possibly reduces lopinavir and ritonavir levels by about 30% (1 Class II study).

Valproic acid possibly increases zidovudine exposure (1 Class II study).

Valproic acid possibly has no effect on efavirenz exposure (1 Class II study).

Ritonavir/atazanavir possibly reduces lamotrigine exposure by about 30% (1 Class II study).

Raltegravir and atazanavir possibly have no effect on lamotrigine exposure (1 Class II study).

Raltegravir possibly has no effect on midazolam exposure (1 Class II study).

The evidence is insufficient to support or refute other pharmacokinetic AED-ARV interactions (single Class III/multiple Class IV studies).

Coadministration of highly active antiretroviral therapy containing a PI or NNRTI and an EI-AED possibly results in higher virologic failure rates (1 Class II study).

**RECOMMENDATIONS** Patients receiving phenytoin may require a lopinavir/ritonavir dosage increase of about 50% to maintain unchanged serum concentrations (Level C).

Patients receiving valproic acid may require a zidovudine dosage reduction to maintain unchanged serum zidovudine concentrations (Level C).

Coadministration of valproic acid and efavirenz may not require efavirenz dosage adjustment (Level C).

Patients receiving ritonavir/atazanavir may require a lamotrigine dosage increase of about 50% to

maintain unchanged lamotrigine serum concentrations (Level C).

Coadministration of raltegravir or atazanavir and lamotrigine may not require lamotrigine dosage adjustment (Level C).

Coadministration of raltegravir and midazolam may not require midazolam dosage adjustment (Level C).

Patients may be counseled that it is unclear whether dosage adjustment is necessary when other AEDs and ARVs are combined (Level U).

It may be important to avoid EI-AEDs in people on ARV regimens that include PIs or NNRTIs, as pharmacokinetic interactions may result in virologic failure, which has clinical implications for disease progression and development of ARV resistance. If such regimens are required for seizure control, patients may be monitored through pharmacokinetic assessments to ensure efficacy of the ARV regimen (Level C).

**CLINICAL CONTEXT** A retrospective cohort study and numerous pharmacokinetic studies indicate that EI-AEDs interact with ARVs. The optimal choice of epilepsy treatment in patients with HIV should reflect an accounting for the metabolic and inhibitory/inducing profiles of coadministered drugs. Clinicians who prescribe ARVs and AEDs are encouraged to refer to the Department of Health and Human Services treatment guidelines for HIV/AIDS, which provide specific recommendations for the management of possible drug–drug interactions with AED-ARV combinations (available at <http://aidsinfo.nih.gov/contentfiles/AdultandAdolescentGL.pdf>). For newer ARV agents, minimal data exist on drug interactions with AEDs.

**RECOMMENDATIONS FOR FUTURE RESEARCH** Future research regarding AED-ARV interactions is needed. Special priority should be given to the study of first-line AED-ARV combinations used in low- and middle-income countries where second-line agents may not be available.

#### **AUTHOR CONTRIBUTIONS**

Dr. Birbeck: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, acquisition of data, study supervision, obtaining funding. Dr. French: drafting/revising the manuscript, study concept or design, analysis or interpretation of data. Dr. Perucca: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, acquisition of data. Dr. Simpson: drafting/revising the manuscript, study concept or design, analysis or interpretation of data. Dr. Framow: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, acquisition of data. Dr. George: drafting/revising the manuscript, analysis or interpretation of data. Dr. Okulich: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, acquisition of data. Dr. Clifford: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, acquisition of data. Dr. Hachad: drafting/revising the manuscript, analysis or interpretation of data. Dr. Levy: analysis or interpretation of data, advising personnel.

## DISCLOSURE

Dr. Birbeck serves on the editorial boards of *Epilepsia* and *Epilepsy & Behavior*; and receives/has received research support from the NIH, the Doris Duke Charitable Foundation, the Dana Foundation, and the Rockefeller Brothers Fund. Dr. French has served on scientific advisory boards for UCB, Johnson & Johnson, Eisai Inc., Novartis, Valeant Pharmaceuticals International, Icagen, Inc., Intranasal Therapeutics Inc., Sepracor Inc., and Marinus Pharmaceuticals, Inc.; has received funding for travel from UCB, Kyowa Hakko Kirin Pharma, Inc., Eisai Inc., Johnson & Johnson, Valeant Pharmaceuticals International, and GlaxoSmithKline; serves as an Associate Editor for *Epilepsy Currents* and the supplements editor for *Epileptic Disorders*; is president of the Epilepsy Study Consortium, which receives money from multiple pharmaceutical companies; 25% of her salary is paid to NYU by the consortium; and she has received research support from SK Pharma Co., Ltd., Valeant Pharmaceuticals International, Pfizer Inc, UCB, Eisai, Johnson & Johnson, the NIH, and the Epilepsy Research Foundation. Dr. Perucca serves on scientific advisory boards for and has received funding for travel or speaker honoraria from Bial, Eisai Inc., GlaxoSmithKline, Johnson & Johnson, Novartis, Pfizer Inc, Vertex Pharmaceuticals, UCB, and Upsher-Smith Laboratories, Inc.; serves on editorial advisory boards for *Epilepsia*, *Acta Neurologica Scandinavica*, *CNS Drugs*, *Epileptic Disorders*, *Epilepsy Research*, *Seizure*, *Lancet Neurology*, *Expert Reviews in Neurotherapeutics*, *Clinical Pharmacokinetics*, *Therapeutic Advances in Drug Safety and Clinical Drug Investigation*, *European Neurological Journal*, *Neurosciences*, and *World Journal of Pharmacology and Clinical Investigation*; receives publishing royalties for *Antiepileptic Drugs* (Raven Press/Lippincott, 2002), *Epilepsy: A Comprehensive Textbook* (Lippincott, 2008), and *The Treatment of Epilepsy* (Wiley Blackwell, 2009); serves as a consultant for Bial, Eisai Inc., GlaxoSmithKline, Ibsa, Johnson & Johnson, Pfizer Inc, sanofi-aventis, SK Holdings Co Ltd, UCB, Supernus Pharmaceuticals, Inc., Vertex Pharmaceuticals, Medtronic, Inc., World Health Organization, and Upsher-Smith Laboratories, Inc.; receives research support from UCB, European Commission, Italian Medicines Agency, Italian Ministry of Health, Italian Ministry for Education, and Institute of Neurology IRCCS C. Mondino Foundation, Pavia, Italy; and prepared an affidavit in a medical-legal case. Dr. Simpson serves/has served on scientific advisory boards for Cephalon, Inc., MEDA Pharmaceuticals Inc., Endo Pharmaceuticals, NeurogesX, Eli Lilly and Company, Pfizer Inc, GlaxoSmithKline, Allergan, Inc., Merz Pharmaceuticals, LLC, Merck Serono, Covidien, Astellas Pharma Inc., Alpharma, Biogen Idec, Ipsen, Gilead Sciences, Inc., Forest Laboratories, Inc., and Acorda Therapeutics Inc.; serves on the editorial boards of *Clinical Journal of Pain* and *AIDS Patient Care*; has served on the speakers' bureau for Eli Lilly and Company and GlaxoSmithKline; serves as a consultant for NeurogesX, Eli Lilly and Company, GlaxoSmithKline, Allergan, Inc., Merz Pharmaceuticals, LLC, Astellas Pharma Inc., Ipsen, and US WorldMeds, LLC.; has received speaker honoraria from Eli Lilly and Company, GlaxoSmithKline, Allergan, Inc., and Astellas Pharma Inc.; receives research support from NeurogesX, Pfizer Inc, Allergan, Inc., Eli Lilly and Company, the NIH (NINDS, NIMH), and the Peripheral Neuropathy Foundation; and has given expert testimony regarding a case involving the myotoxicity of statins. Dr. Fraimow has received research support from JMI Laboratories and the NIH. Dr. Fraimow's spouse has served on scientific advisory boards for UCB, Johnson & Johnson, Eisai Inc., Novartis, Valeant Pharmaceuticals International, Icagen, Inc., Intranasal Therapeutics Inc., Sepracor Inc., and Marinus Pharmaceuticals, Inc.; has received funding for travel from UCB, Kyowa Hakko Kirin Pharma, Inc., Eisai Inc., Johnson & Johnson, Valeant Pharmaceuticals International, and GlaxoSmithKline; serves as an Associate Editor for *Epilepsy Currents* and the supplements editor for *Epileptic Disorders*; is president of the Epilepsy Study Consortium, which receives money from multiple pharmaceutical companies; 25% of her salary is paid to NYU by the consortium; and she has received research support from SK Pharma Co., Ltd., Valeant Pharmaceuticals International, Pfizer Inc, UCB, Eisai, Johnson & Johnson, the NIH, and the Epilepsy Research Foundation. Dr. George served on a scientific advisory board for Pfizer Inc. Dr. Okulicz reports no disclosures. Dr. Clifford serves/has served on scientific advisory boards for Biogen Idec, Elan Corporation, Roche, Forest Laboratories, Inc., Genentech, Inc., GlaxoSmithKline, Millennium Pharmaceuticals, Inc., Schering-Plough Corp., Bristol-Meyers Squibb, and Genzyme Corporation; re-

ceived speaker honoraria and funding for travel from GlaxoSmithKline, Millennium Pharmaceuticals, Inc., and Genentech Inc.; has received research support from Pfizer Inc, Schering-Plough Corp., Bavarian Nordic, NeurogesX, GlaxoSmithKline, Tibotec Therapeutics, Boehringer Ingelheim, and Gilead Sciences, Inc.; and receives research support from the NIH (NIMH, NINDS, NIAID, and Fogarty Institutes). Dr. Hachad reports no disclosures. Dr. Levy serves on the editorial advisory board for *Drug Metabolism Letters*; has served as a consultant for Johnson & Johnson, Neurocrine Biosciences, Inc., Xenon, Biocodex, NeuroAdjuvants Inc., Allergan, Inc., Jazz Pharmaceuticals, and NeuroVista Corporation; has received publishing royalties for *Antiepileptic Drugs*, 5<sup>th</sup> ed. (Lippincott Williams & Wilkins, 2002); and has served as an expert witness in medical-legal cases.

## DISCLAIMER

This statement is provided as an educational service of the American Academy of Neurology and the International League Against Epilepsy (ILAE). It is based on an assessment of current scientific and clinical information. It is not intended to include all possible proper methods of care for a particular neurologic problem or all legitimate criteria for choosing to use a specific procedure. Neither is it intended to exclude any reasonable alternative methodologies. The AAN and ILAE recognize that specific patient care decisions are the prerogative of the patient and the physician caring for the patient, based on all of the circumstances involved. The clinical context section is made available in order to place the evidence-based guideline(s) into perspective with current practice habits and challenges. No formal practice recommendations should be inferred.

## CONFLICT OF INTEREST

The American Academy of Neurology is 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 keeps 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. AAN limits the participation of authors with substantial conflicts of interest. The AAN forbids commercial participation in, or funding of, guideline projects. Drafts of the guideline have been reviewed by at least three AAN 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](http://www.aan.com).

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International League Against Epilepsy**

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