



AEDs and Cognition: One Small Fish in a Very Large Pond?

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Antiepileptic Drugs Are Not Independently Associated With Cognitive Dysfunction

Foster E, Malpas CB, Ye K, et al. *Neurology*. 2020;94:e1051-e1061. doi:10.1212/WNL.0000000000009061.

Objective: To test the hypothesis that individual antiepileptic drugs (AEDs) are not associated with cognitive impairment beyond other clinically relevant factors, we performed a cross-sectional study of patients admitted to an inpatient video-electroencephalogram monitoring unit. **Methods:** We prospectively enrolled patients admitted to an inpatient specialist epilepsy program between 2009 and 2016. Assessments included objective cognitive function, quality of life subscales for subjective cognitive function, and questionnaires for anxiety and depressive symptoms. Bayesian model averaging identified predictors of cognitive function. Bayesian model selection approach investigated effect of individual AEDs on cognition. Conventional frequentist analyses were also performed. **Results:** A total of 331 patients met inclusion criteria. Mean age was 39.3 years and 61.9% of patients were women. A total of 45.0% of patients were prescribed AED polypharmacy, 25.1% AED monotherapy, and 29.9% no AED. Age, seizure frequency, and a diagnosis of concomitant epilepsy and psychogenic nonepileptic seizure were predictors of objective cognitive function. Depression, anxiety, and seizure frequency were predictors of subjective cognitive function. Individual AEDs were not independently associated with impaired cognitive function beyond other clinically relevant variables. **Conclusions:** This study found that no AED was independently associated with cognitive dysfunction. Significant determinants of objective and subjective cognitive dysfunction included seizure frequency and depression, respectively. These findings suggest that optimizing therapy to prevent seizures is not likely to occur at the expense of cognitive function.

Commentary

For over a century, medications used to treat epilepsy have been known to occasion instances of positive (ie, seizure reduction) and at times negative effects upon cognition.¹ Over the past 3 decades, numerous clinical trials have included the assessment of cognitive function as a standardized outcome measure when assessing efficacy, tolerability, and safety of old line and newer antiepileptic drugs (AEDs).² The impact of AED adverse events (including cognition) has consistently been included when establishing quality metrics for epilepsy care.³ It's with these efforts that medical professionals working with persons with epilepsy have striven toward the treatments goals of seizure freedom and maximizing reduction in seizures while minimizing adverse events.

Despite best intended current practice efforts, AED cognitive side effects do occur. However, a question remains under what circumstances? With this in mind, Foster and colleagues⁴ recently examined this challenging question. They examined extent to which AEDs, within a clinical constellation of medical and demographic features, contributed to the cognitive status of a heterogeneous sampling of adults undergoing inpatient video-electroencephalogram (EEG) monitoring. Their

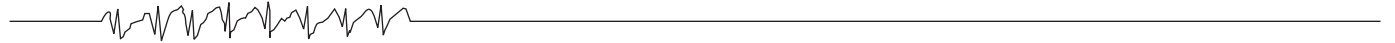
contention was that AEDs were not independently associated with objective or subjective cognitive function after factoring in the other examined factors.

However, as mentioned above, AEDs have long had the attention of clinicians and researchers as to their potential affects upon cognitive functioning.⁵ I quote from Hermann & Loring's *Neurology* Editorial that commented on the Foster et al study because I could not state it any clearer "an arguably striking dichotomy exists between the extant literature and this report."

Foster and colleagues assessed cognitive status using a psychometrically established screening measure administered to a sample of over 300 adults (epilepsy, PNES, nondiagnostic groups) being evaluated at a large medical center inpatient video/EEG monitoring unit. They employed sophisticated Bayesian probability modeling to establish a set of predictors of cognitive function that included a secondary examination of cognitively "dirty" versus "clean" AED groups with topiramate, zonisamide, phenytoin, and oxcarbazepine setting the "dirty" group. They found that no individual AED, AED combination, or "dirty" AED group were predictors of patient cognitive test performance. They did find that being older and



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having more seizures were predictive of poorer cognitive status. The authors concluded that these findings “may reassure patients and clinicians that the real-world effect of topiramate” (and other AEDs) “may not be as substantial as the literature suggests.” The authors pointed out that factors such as lower AED dosages and higher premorbid cognitive attainment may reduce potential of untoward cognitive effects. The authors readily acknowledged study limitations including characterizing seizure frequency estimates retrospectively, as well as the use of a cognitive screening measure that may not be as sensitive as a more extensive cognitive battery.

Without intended overlap with the aforementioned Hermann & Loring’s Editorial comment, I make a few specific points and general comments.

The authors conducted the study within an inpatient Epilepsy Monitoring Unit (EMU) setting. They appropriately pointed out positives for this strategy. However, common goals for EMU monitoring are to capture seizures for diagnostic and treatment purposes. Eliciting seizures are often accomplished via reduction in AED medications prior to or at the time of EMU monitoring. The study findings may have been directly affected by a clinical shifting in the strength of 2 of their predictor factors (ie, increasing seizure frequency/recency while at the same time reduction in another [ie, AED dose]). Thus, within the EMU setting, in contrast to an outpatient setting, there could incur a resulting increased seizure frequency as a function of AED medication reduction to maximize the time-limited recording opportunities in the EMU setting.

It was not clear how the authors accounted for this issue. It may not have significantly affected their findings but may have made it more difficult to detect an “AED cognitive effect signal” that may more clearly occur in the course of a patient’s non-EMU treatment course. Although the authors acknowledged that AEDs were “reduced or ceased during admission to optimize seizure yield”^(p e1053) they did not specify further details. Although they listed several AEDs examined, no mention was made of individual AED dose ranges prior to or at time of EMU monitoring. It seems important to know how many AEDs were reduced or ceased at time of the cognitive testing. It also seems possible that within an outpatient setting AED dosing was higher and more complex (eg, taking polytherapy that was reduced to monotherapy at time of EMU admission). There exist prior studies demonstrating that AED dose load does matter when examining cognitive impacts, especially for drugs such as topiramate.^{6,7}

There exist over 30 years of clinical and controlled trial studies focused at sorting out AED efficacies and adverse effects. These trials have contributed to changes in “real world” practice by encouraging slower titration schedules, avoidance of potential iatrogenic drug interactions, favoring new line over old line medications when possible, and by monitoring AED adverse event profiles which in turn positively impacts patient quality of life.⁸ With these standards of care³ in mind, it may be that patients such as those admitted to an EMU setting had reduced AED burden that could affect cognitive function. For

example, it was noteworthy that from the 273 instances of AED medications (ie, 25% monotherapy, 45% polytherapy, 30% no AED) in the study, 75% were taking “clean” medications. Thus, positively highlighting that treating physicians sending their patients to the EMU were attending to key treatment goals of maximizing AED efficacy and minimizing adverse event potential.

The authors listed carbamazepine in their “clean” medication group but had phenytoin and valproate in the “dirty” group. However, prior controlled studies have found similar cognitive profiles between these medications.⁵ That review study also highlighted that carbamazepine had a poorer cognitive profile compared to levetiracetam in 2 controlled studies. This is relevant since the present study listed levetiracetam as the most commonly administered AED followed by valproate and carbamazepine. Operto et al⁹ recently described cognitive effects (ie, changes in executive function) of various AED treatments in new-onset/drug naive pediatric epilepsy patients over a 9-month period. Results found the only AED examined with positive cognitive impact was levetiracetam, while carbamazepine as the only AED showing negative test performance.

The authors acknowledge that their cognitive screening measure had “minimal dependency on reaction time or processing speed.” Historically, reduced psychomotor speed with certain AEDs have been cited concerns. The present study was not able to address that issue specifically. However, recent work has suggested that AED cognitive effects may relate more to “higher-order cognitive processing” rather than psychomotor speed/reaction time measures.¹⁰ The NUCOG has elements of that higher order functioning (ie, tasks of fluency generation, digit spanning) similar to that of Helmstaedter’s NeuroCog Function battery.¹⁰ However, further work anticipated to help better understand the specific cognitive impacts for AED pharmacotherapy.


The authors noted the complexity understanding the role AEDs play in epilepsy-related cognitive status. The authors tackled a tough opponent and addressed via a solid statistical methodology teasing out contributions from many factors such as neurodevelopment history, AEDs, seizure type/frequency all likely contributing to unique individual patient-centered synergistic effects.¹¹

In sum, it seems that the question is not whether various AEDs have potential untoward cognitive effects, as several certainly do,⁸ but how and under what circumstances these effects present themselves, are subsequently minimized, and acknowledging that other factors are just as impactful or even more so. At the same time, it is important to keep in mind that AEDs can positively contribute to cognitive effects via reduction in seizure frequent/severity.


Foster and colleagues⁴ study findings are overall encouraging from the standpoint of finding limited association between AEDs and cognitive function. Their findings may have reflected the positive impact of current clinical practice patterns for prudent AED selection, dosing, and side effect monitoring that has positively reduced the incidence of AED-induced cognitive



effects. It may be a function of the increased awareness within the epilepsy and broader medical community.

By Roy C. Martin 

ORCID iD

Roy C. Martin  <https://orcid.org/0000-0001-9328-0846>

References

1. Loring DW, Hermann BP. History of epilepsy neuropsychology. In: Barr WB, Bieliauskas LA, eds. *The Oxford Handbook of History of Clinical Neuropsychology*. Oxford University Press; 2018.
2. American Epilepsy Society. *Current Review in Clinical Science: Summary of Antiepileptic Drugs*; 2018. www.aesnet.org
3. Pugh MJV, Berlowitz DR, Montoruis G, et al. What constitutes high quality of care for adults with epilepsy? *Neurology*. 2007; 69(1):2020-2027.
4. Foster E, Malpas CB, Ye K, et al. Antiepileptic drugs are not independently associated with cognitive dysfunction. *Neurology*. 2020;94(10):e1051-e1061. doi:10.1212/WNL.0000000000009061.
5. Loring DW, Marino S, Meador KJ. Neuropsychological and behavioral effects of antiepilepsy drugs. *Neuropsychol Rev*. 2007;17(2):413-425.
6. Witt J, Elger CE, Helmstaedter C. Adverse cognitive effects of antiepileptic pharmacotherapy: each additional drug matters. *Eur Neuropsychopharmacol*. 2015;25(1):1954-1959.
7. Loring DW, Williamson DJ, Meador KJ, Wiegand F, Hulihan J. Topiramate dose effects on cognition: a randomized double-blind study. *Neurology*. 2011;76(1):131-137.
8. Witt J, Helmstaedter C. How can we overcome neuropsychological adverse effects of antiepileptic drugs? *Expert Opin Pharmacother*. 2017;18(6):551-554.
9. Operto FF, Pastorino GMG, Mazza R, et al. Effects on executive functions of antiepileptic monotherapy in pediatric age. *Epilepsy Behav*. 2020;102:106648.
10. Helmstaedter C, Durch P, Hoppe C, Witt J. Is the computerized assessment of psychomotor speed more sensitive to cognitive effects of antiepileptic pharmacotherapy than tests with a focus on higher-order cognitive processes? implications for the choice of sensitive test parameters. *Eur Neuropsychopharmacol*. 2019;29(3):1273-1281.
11. Witt J, Helmstaedter C. Monitoring the cognitive effects of antiepileptic pharmacotherapy—approaching the individual patient. *Epilepsy Behav*. 2013;26(2):450-456.