

Review

Cognition across the lifespan: Antiepileptic drugs, epilepsy, or both?

Bruce Hermann^a, Kimford J. Meador^b, William D. Gaillard^c, Joyce A. Cramer^{d,*}^a University of Wisconsin, Madison, WI, USA^b Emory University, Atlanta, GA, USA^c Childrens' Medical Center, Washington, DC, USA^d Epilepsy Therapy Project and Yale University, Houston, TX, USA

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ABSTRACT

Cognitive problems in persons with epilepsy manifest over a lifetime; however, whether abnormal cognition in an individual with epilepsy is a result of comorbid brain substrate, the epilepsy itself or its underlying etiology, the antiepileptic agents used to control it, or a combination of these and other factors remains controversial. There is a continuing need for improved therapies to control seizures and reduce the incidence of adverse events, especially those involving the central nervous system that compromise attention, intelligence, language skills, verbal and nonverbal memory, executive function, and psychomotor speeds. Although cognitive decline typically occurs among patients with more severe epilepsy, physicians must judiciously select therapy with an eye toward not only controlling seizures but also ensuring that all patients retain as much function as possible throughout their lives.

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1. Cognition across the lifespan

Cognition comprises a broad range of functions, such as attention, intelligence, visual memory, and fine motor dexterity (Table 1). Abnormalities in cognition are commonly reported in people with epilepsy. Problems with cognition can be manifested as reductions in attention, IQ, language and perceptual skills, executive functions including problem solving, verbal and visual memory, motor speed, dexterity, and coordination. The poorest cognition is associated with early age at onset and, thus, longer duration of epilepsy, especially in the presence of generalized tonic-clonic seizures, repeated episodes of status epilepticus, and increased exposure to antiepileptic drugs (AEDs).

The most common focal seizures begin in the temporal lobe and immediate structures, so memory problems are likely to be anticipated in people with temporal lobe epilepsy (TLE). The major site of seizure onset associated with TLE is within the mesial temporal lobes, and significant volumetric abnormalities extend beyond the primary epileptogenic region. Initially, studies concentrated primarily on the hippocampus, given the importance of that structure in TLE, but abnormalities have been found to be distributed over a wider neural network.

Using high-resolution MRI, researchers have performed volumetric measurements to assess patients with TLE. Bernasconi and colleagues confirmed that pathological findings of damage in the mesial temporal lobe involve the hippocampus, the amygdala, and the entorhinal and perirhinal cortices; damage in all these structures was caused by cell loss in entorhinal-hippocampal connections resulting from electrical activity between the two structures [1]. At the same institution, an earlier study had established that there was a bilateral reduction in the volume of the entorhinal cortex in patients with TLE when compared with a control group; however, the statistically significant reduction in volume of the entorhinal cortex was more severe ipsilateral to the epileptic focus [2]. When Kuzniecky et al. performed volumetric measurements of the hippocampus, amygdala, fornix, and mamillary bodies in 50 patients with mesial TLE and compared the results with those of normal controls, the data showed that atrophy in mesial TLE is not limited to the hippocampus, but also occurs in other limbic systems; normalized fornix volumes showed atrophy in 86% of studies concordant with hippocampal atrophy [3]. Natsume and colleagues evaluated patients with TLE whose seizures were intractable to pharmacotherapy, comparing them with patients with extratemporal lobe epilepsy (ETE), idiopathic generalized epilepsy (IGE), and controls without epilepsy. Thalamic volumes did not significantly differ between patients with ETE and IGE; however, patients with TLE had reduced volume ipsilateral to the seizure focus. Moreover, thalamic atrophy in patients with TLE is correlated with disease duration [4]. As might be expected given MRI findings such as these,

* Corresponding author. Address: Epilepsy Therapy Project and Yale University, 49 Briar Hollow Lane, No. 1804, Houston, TX 77027, USA. Fax: +1 713 552 0289.

E-mail addresses: joyce@epilepsytherapyproject.org, joyce.cramer@yale.edu (J.A. Cramer).

Table 1
Cognitive domains.

Domain	Ability
Attention	Vigilance Dual task processing
Intelligence	Verbal Nonverbal
Language	Confrontation naming Verbal fluency
Visuoperceptual	Facial discrimination Spatial judgment
Verbal memory	Auditory memory—immediate Auditory memory—delayed
Nonverbal memory	Visual memory—immediate Visual memory—delayed
Executive function	Problem solving Response inhibition Speeded psychomotor Working memory
Motor	Speeded psychomotor Speeded fine motor dexterity

when cognition is examined comprehensively in patients with chronic TLE, cognitive abnormalities often extend beyond the area of memory function [5].

Recent literature has provided additional examples of neuro-anatomic abnormalities in patients with chronic epilepsy. In a study by Lin and colleagues, a cohort of individuals with mesial TLE and documented hippocampal sclerosis, evaluated with preoperative high-resolution MRI, had evidence of distributed cortical thinning that was evident not only ipsilaterally but also contralateral to the site of seizure onset [6]. The subjects showed up to 30% bilateral decrease of cortical thickness in the temporal, parietal, occipital, and frontal lobes. Longer duration of epilepsy was linked to greater thickness reduction in the superior frontal and parahippocampal gyrus ipsilateral to the side of seizure onset. The bilateral distribution in both the temporal and extratemporal regions again bears resemblance to a pattern of generalized cognitive impairment [6].

What is the cause of cognitive deficits in chronic epilepsy? A 4-year prospective study of 46 individuals with chronic TLE and 65 control subjects evaluated the ability of baseline MRI characteristics, demographic information, and clinical presentation of epilepsy to predict abnormalities in cognitive trajectory [7]. Patients were on average 33 years of age and had durations of epilepsy ranging from 17 to 20 years. The prospective cognitive trajectory of the chronic epilepsy group was quite different from that of controls. Approximately 10% to 30% of patients had abnormal trajectories in IQ, language, perception, memory, executive skills, and motor coordination, thus demonstrating greater adverse cognitive changes compared with control subjects over the 4-year period. Baseline volumetric abnormalities and lower IQ, which indicate increased cognitive vulnerability, were the strongest predictors of lower cognitive stability in these patients. Consequently, baseline volumetric abnormalities not only were associated with cognition on a cross-sectional level, but were also predictive of an increased risk of a progressively abnormal cognitive course. The more traditional variables, such as duration, age at onset, and education, were less predictive than baseline volumetric abnormalities and lower IQ; in contrast, seizure frequency and medication were the least predictive variables [7].

2. Effects of a disordered substrate

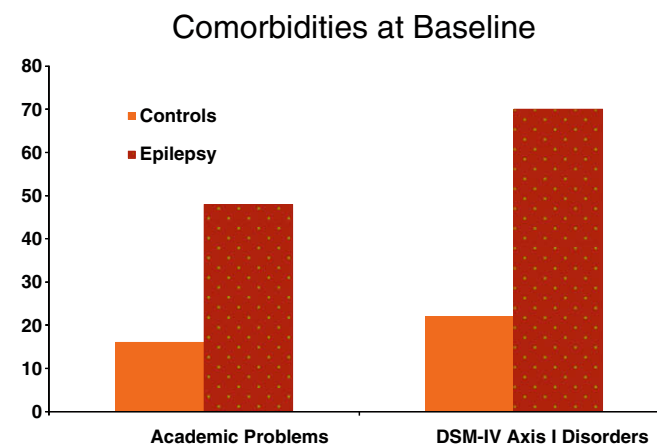
When does this cognitive difficulty originate? Studies examining the nature of cognitive abnormalities in epilepsy have shown that neuropsychological disruption can be detected at or near the onset of epilepsy in children with a diversity of epilepsy syndromes

[8–13]. How cognitive problems worsen over time in a neurodevelopmental context remains to be clarified. It is certainly clear that children with even short durations of epilepsy may exhibit considerable cognitive abnormalities, which again points to a neurodevelopmental contribution. For example, Schoenfeld and colleagues studied a cohort of 57 children with chronic complex partial seizures, primarily the temporal lobe type [14]. The control group consisted of 27 unaffected siblings. The children with epilepsy underperformed their siblings in all aspects: verbal and nonverbal memory, language, academic achievement, problem solving, mental efficiency, and motor skills. In a similar study, Caplan and colleagues [15] examined 69 children with chronic absence epilepsy and compared them with age- and gender-matched controls. Despite a mean IQ in the normal range, one-fourth of the children with epilepsy had subtle cognitive difficulties, nearly one-half had linguistic difficulties, and nearly two-thirds had psychiatric diagnoses. Only 23% of the children with epilepsy had intervention for their difficulties, indicating the need for early identification and treatment [15].

Cognitive [12,16–18] and psychiatric [11,19–21] difficulties exist before the first recognized seizure and are therefore independent of medications, seizures, and social reactions to seizures. A study conducted at the University of Wisconsin showed that nearly 50% of patients with new-onset epilepsy reported academic problems, and an even higher proportion presented with DSM-IV Axis 1 lifetime-to-date disorders (Fig. 1) [12,19]. It is important, however, to keep in mind that not only is there wide variability between patients based on the type and severity of epilepsy, but there are also a wide variety of non-seizure-related and treatment-related factors. Clinicians often confine themselves to the latter.

3. Effects of treatment on cognition

Similar to drugs like alcohol, AEDs are more likely to have adverse cognitive effects at higher doses, higher blood levels, or rapid upward titration. In addition, taking several different AEDs has an additive effect, increasing toxicity. Similar to chronic alcohol consumption, habituation of some cognitive effects occurs with AEDs over time. When an AED is first initiated, cognitive side effects are more likely to occur, and adverse effects lessen after a period of 3 to 4 weeks. Like the person who has become habituated to alcohol, patients may experience cognitive side effects from AEDs without being aware of it. There are differences in adverse cognitive effects between AEDs, and individual patients differ in susceptibility to and metabolism of AEDs.



Jones et al., 2005; Hermann et al., 2006

Fig. 1. Comorbidities at baseline [12,19].

4. Older versus newer AEDs

When patients with epilepsy are treated with AEDs, their seizures are reduced, and the improvement in the patient's cognition from reduced seizures may often offset, at least in part, the underlying cognitive side effects of the AEDs. To avoid the confounding effects on cognition resulting from changes in seizure frequency, Meador and colleagues recruited healthy adults for a series of studies that compared the differential and behavioral effects of AEDs [22–24]. This approach also allows extrapolation of the findings to patients taking AEDs for other indications such as psychiatric or pain disorders. The researchers performed neuropsychological evaluations to measure variables (e.g., finger tapping, choice reaction time, grooved pegboard, memory performance) of study subjects at baseline, during or immediately after treatment, and at least 1 month after initiation of treatment, depending on study protocols. Data from the studies indicated that three older AEDs (carbamazepine, phenytoin, and valproate) were very similar (90–96%) with respect to their effects on attention, motor speed, and memory, despite their unique profiles for epilepsy efficacy and varying psychotropic effects [22–24]. Among the older drugs, phenobarbital was an exception. About one-third of the variables were significantly worse with phenobarbital at low blood levels compared with midrange blood levels of phenytoin or valproate [24].

Similar studies have been conducted for some of the newer AEDs [25–30]. Lamotrigine, levetiracetam, and gabapentin resulted in 48%, 42%, and 26% fewer cognitive side effects, respectively, compared with carbamazepine. Oxcarbazepine, although better tolerated than carbamazepine and phenytoin, showed no differences compared with phenytoin in formal neuropsychological testing. Not all the new drugs have lower cognitive profiles. Topiramate, when tested against gabapentin and lamotrigine, significantly worsened cognitive side effects.

Processing speed (reaction time) and complex or sustained attention are the variables most susceptible to AEDs. Dual processing was also strongly affected. Verbal learning—in particular, recall of paragraphs—was more vulnerable than word lists because paragraph recall requires a higher attention component. Verbal fluency (rate at which words beginning with a specific letter or from a specific category can be generated) can be affected by some drugs (e.g., topiramate and carbamazepine). During the studies of older and newer AEDs, subjects underwent memory testing (Medical College of Georgia Paragraph Memory) to compare performance on each AED with nondrug performance (Fig. 2) [22,23,25–27].

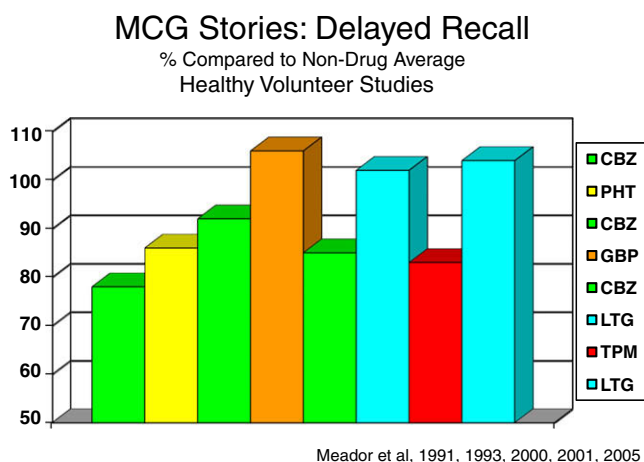


Fig. 2. Medical College of Georgia Paragraph Memory: Delayed Recall [22,23,25–27].

Gabapentin and lamotrigine did not affect memory recall on the paragraph memory test, but carbamazepine, phenytoin, and topiramate reduced the number of items recalled by 10% to 20%. In a classroom or an office setting that requires a high degree of attention and memory performance, losing 10% to 20% of one's cognitive function will severely and negatively affect quality of life.

Gilliam and colleagues found a very high correlation between subtle toxic effects and patients' perceived quality of life [31]. This study was conducted in tertiary epilepsy centers, where patients were not grossly toxic. Even in that setting, half the patients scored higher on the adverse events profile summary scale, which assesses symptoms related to central toxicity. An increasing score on the toxicity measure was associated with progressive decline in subjects' perceived quality of life.

5. Age-related effects

There are also age-related differences with respect to cognitive effects. Unfortunately, there are few data on the cognitive effects of AEDs in the elderly, even though the elderly are especially sensitive to central nervous system (CNS) effects of drugs for both pharmacokinetic and pharmacodynamic reasons. Craig and Tallis found no differences when comparing the effects of phenytoin and valproate on cognitive functioning in elderly patients with epilepsy [32]. Reanalysis of the original Veterans Affairs (VA) Cooperative Study revealed that elderly veterans had increased sensitivity to the CNS toxic side effects of carbamazepine, phenobarbital, phenytoin, and primidone; however, patients generally responded well to the drugs [33]. Older patients are particularly vulnerable because of physiological changes caused by aging, reduced metabolic rate for AEDs, and increased risk of drug–drug interactions from taking multiple medications. The implication from these findings is that using a lower dosage and aiming for a lower therapeutic blood range would be more appropriate for older patients than using a standard dosing and striving for standard blood levels for these older AEDs. In a separate VA Cooperative Study, Rowan and colleagues conducted a cooperative, randomized study at 18 VA medical centers to examine comparative tolerability and efficacy of gabapentin, lamotrigine, and carbamazepine [34]. There were 592 patients, 65 years or older, with new-onset epilepsy enrolled, and each patient remained on one of the three assigned AEDs until the end of the study. Patients who were placed on lamotrigine or gabapentin tolerated the drug better and stayed on the drug longer than did patients who were treated with carbamazepine [34].

With respect to cognitive side effects, data in children are limited, but they tend to mirror the information for healthy volunteers [35]. Meador and colleagues examined the effects of four commonly used drugs—carbamazepine, lamotrigine, phenytoin, and valproate—on cognitive function in children at 3 years of age after fetal exposure to AEDs [36]. Children exposed to valproate had IQs 6 to 9 points lower than did children exposed to the other three drugs. This finding is clearly clinically significant and has major implications with respect to lifetime learning losses.

6. Clinical approaches to treating children

There are a variety of factors in childhood epilepsy that affect cognition, including (1) the underlying developmental substrate, (2) the effect of epilepsy itself on cognition and behavior, and (3) the choice of AED. In children with refractory epilepsy or catastrophic epilepsy, it is very difficult to distinguish these three factors. In children with developmental delays presumed to be a function of seizures, more medication might be provided, which might further affect cognition. Withdrawing a medication can

exacerbate the epilepsy and confound determining to which of the factors it had actually contributed.

Managing children with epilepsy occurs on a background of development that differs from child to child. Children with developmental delays might have trajectories parallel to but lower than a normal trajectory. Some children will plateau in cognition, resulting in a wider gap between themselves and their normal peers. Others will regress and decline, the marker of a degenerative disease. Paying attention to the trajectory is central to caring for children, particularly those with catastrophic epilepsy.

Comorbidity is another factor to consider. Conditions such as attention deficit hyperactivity disorder (ADHD) occur in nearly one-third of these children in addition to anxiety disorders and depression. For a child clearly impaired with ADHD, stimulants are the medication of choice, despite the possible risk of lowering the seizure threshold. Parental anxiety can also exacerbate a child's anxiety. These factors play into the self-esteem of the child and limit the capacity of the child for independence and normal socialization. It is, therefore, important not only to identify comorbid conditions, but also to treat them, as they can compromise a child's quality of life even more so than the seizures themselves.

Few AEDs have been approved by the U.S. Food and Drug Administration for pediatric epilepsy, especially those intended for monotherapy. Furthermore, there are no equivalency data for the epilepsy syndromes that occur in early childhood, and there have been very few efforts to examine the cognitive effects of anti-convulsants in children. Several studies have found that phenobarbital has adverse effects on behavior and cognition [37–39]. Although some studies favor the use of lamotrigine, they do not provide sufficient evidence to guide treatment [39].

7. Catastrophic localization-related epilepsy

Catastrophic localization-related epilepsy occurs in children younger than 2 years of age and results from cortical malformation, stroke, or (in older children) Rasmussen's encephalitis. Epilepsy syndromes such as Dravet's syndrome and severe myoclonic epilepsy of infancy, infantile spasms, and Lennox–Gastaut syndrome are generally localization related. Children with catastrophic epilepsies are generally young and have seizures that occur daily and are associated with a developmental encephalopathy. Outcomes for these children are uniformly poor [40]. Evidence suggests that controlling the seizures with an AED offers a better outcome and may allow the child to experience either a developmental plateau or a reduced decline. Because of the lack of prospective data, it is difficult to assess the effect of an anticonvulsant on development in young children. There is evidence that providing an intervention as early as possible might result in better epilepsy control and long-term outcomes. Surgery should be considered if it involves a clear lesion and if the epileptic condition is refractory, with failure of two or three medications to control the seizures.

8. Infantile spasms

The cognitive outcome for children with infantile spasms is generally very poor. Study data on adrenocorticotropic hormone, prednisone, and vigabatrin are promising. There is some evidence that vigabatrin provides adequate seizure control in infants with tuberous sclerosis and infantile spasms. Only one study has compared medications for both immediate medical effects and long-term developmental outcome [41,42]. Lux and colleagues have demonstrated that steroids offer better short-term control of seizures than does vigabatrin. There does not appear to be any difference among AEDs with respect to long-term cognitive outcomes.

9. Lennox–Gastaut syndrome

Valproate, felbamate, lamotrigine, topiramate, and rufinamide have been shown to be useful in helping to reduce the seizure severity of Lennox–Gastaut syndrome; however, these trials did not examine cognitive improvement [43–46]. In children with Lennox–Gastaut syndrome, successful medical treatment of seizures can improve epileptic encephalopathy, but might result in increased hyperactivity and reduced sleep. Sedative effects on the child are somewhat less disconcerting to parents, unless they clearly interfere with the child's learning abilities or daily life skills.

10. Temporal lobe epilepsy

The original insult from TLE may occur in children younger than 5 years of age, and may be associated with prolonged or focal febrile seizures, meningitis, or encephalitis. The onset of epilepsy from this insult occurs later in childhood (between ages 7 and 9). The seizures are characterized not only by their latency, but also by periods of remission. Targeting treatment for a child with chronic epilepsy, especially when a quiescent period occurs before adolescence, is challenging.

An abnormal MRI or PET scan at the onset of seizures portends a poor outcome [47–50]. Surgery might be the best option for children who have required three or more AEDs to control seizures. Cross-sectional studies provide evidence that some forms of TLE are progressive entities as demonstrated by the continued loss of cerebral glucose utilization and hippocampal volume [51,52]. Finally, there are conflicting data to suggest whether the decline in hippocampal volume and function is related to the seizure count itself [53]. It may be related to the interictal epileptogenic process rather than the seizure count, which would make gauging the success of treatment with AEDs problematic.

11. Summary

Cognition is only one consideration when choosing an AED. Efficacy and other side effects must also be taken into account. Whenever possible, it is prudent to use the lowest effective AED dose, titrate upward slowly, employ monotherapy, and individualize decisions by taking into account patients' reports. Keep in mind, however, that a patient's perception of her or his cognitive side effects might be more related to mood than to actual cognitive performance. Patients who report having trouble with memory might actually be depressed. If there is evidence of a mood disorder, its treatment should be considered. Also, the possibility of drug interactions must be considered, as polytherapy can have a deleterious effect on cognition. Choice of medications should be based on seizure type, and should target the underlying comorbid disorders. It is also important to reassess the severity of the seizures and the efficacy of the AEDs in use, as well as to assess the adverse effects of the disease in addition to the adverse effects of treatment at each visit.

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