



# Cognitive and Behavioral Comorbidities: An Unwanted Effect of Antiepileptic Drugs in Children

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Epilepsy is one of the most common neurological disorders and, despite optimally chosen and dosed antiepileptic drugs (AEDs), approximately 20%-30% of patients will continue to have seizures. Behavior and cognition are negatively impacted by seizures, but AEDs are also a major contributor to behavioral and cognitive deficits. However, the cognitive and behavioral effect of AEDs in children is insufficiently emphasized in the literature. This review summarizes the cognitive and behavioral effects of AEDs in the pediatric population with the objective of helping pediatricians and pediatric neurologists to select the AEDs with the best profile for their individual patient's needs.

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## Introduction

Epilepsy is one of the most common neurological disorders, affecting approximately 41-187/100,000 children per year.<sup>1</sup> Despite optimally chosen and dosed antiepileptic drugs (AEDs), approximately 20%-30% of patients with epilepsy will continue to have more than one seizure per month, of whom 12% will have weekly seizures, and 8% daily seizures.<sup>2-4</sup> They have a negative effect on behavior and cognition<sup>5-7</sup>: seizures in children, especially when persistent, have been associated with reduced working memory and attention.<sup>8,9</sup> In addition to seizures, AEDs are also a major contributor to cognitive and behavioral deficits. As expressed by Lennox, "many physicians in attempting to extinguish seizures only succeed in drowning the finer intellectual processes of their patients."<sup>10</sup> AEDs, especially when in polytherapy, negatively affect executive functions, memory, and behavior.<sup>11-16</sup> Some studies have suggested that this occurs mainly when the plasma levels of AEDs are high, and these studies failed to find adverse cognitive effects when the AEDs levels are in the normal-low

range.<sup>17,18</sup> On the other hand, some AEDs, like lamotrigine (LTG) and levetiracetam (LEV), have a favorable cognitive profile preferable in patients with existing cognitive deficits, although LEV may have prominent behavioral side effects.<sup>12,13,19</sup> The behavioral and cognitive effect of AEDs is intertwined with that of seizures and several other factors might also affect cognition and behavior, such as epilepsy etiology, age at onset of seizures, seizure type, frequency, and duration and electroencephalographic pattern. However, AEDs might account for some independent effect as shown in a study of 301 patients who underwent neuropsychological assessment before and some period after epilepsy surgery.<sup>20</sup> In this study, start of AED withdrawal, number of AEDs reduced, and complete AED withdrawal were associated with improved postoperative intelligence quotient (IQ) scores and gain in IQ, independent of other determinants of cognitive outcome.<sup>20</sup>

There is limited literature on the effects of AEDs on behavior and cognition in children. Unfortunately, the few existing studies on this topic have heterogeneous designs and small sample sizes. This review will emphasize the importance of considering behavioral and cognitive effects when selecting AEDs in children, as well as the importance of regularly measuring behavioral and cognitive function in children on AEDs. The objective of this review is to summarize the effects of the most commonly used AEDs on cognition and behavior in children and adolescents to help pediatricians and pediatric neurologists to select the AEDs with the best cognitive and behavioral profile for their individual patient's needs.

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## Carbamazepine

The main mechanism of action of carbamazepine (CBZ) is sodium channel blockage and it is used principally for focal seizures.<sup>21-23</sup> A study evaluated 7 children with symptomatic focal epilepsy, no electroencephalographic anomalies for at least 1 year and no seizures for at least 2 years before and at least 12 months after discontinuation of CBZ.<sup>16</sup> In this small series, CBZ did not appear to affect memory, intellect or attentional functions, but when suspended, executive functions significantly improved, suggesting that CBZ makes some complex behaviors less efficient than they could have been.<sup>16</sup> In another study, 5 children with rolandic epilepsy not on CBZ scored higher on wide assessment of memory and learning-story memory compared with 5 children with rolandic epilepsy receiving CBZ.<sup>24</sup> On the other hand, in a series of 45 children with epilepsy and learning or behavioral problems—in part due to sedative AEDs—patients showed significant cognitive improvement and greater alertness when CBZ was started and all or some of the original AEDs discontinued.<sup>22</sup> This effect was probably combined due to better seizure control, discontinuation of sedating AEDs, and even practice or learning effects in previously administered tests. In a study of 11 patients, higher blood levels of CBZ correlated with lower memory performance but higher performance on the Purdue Pegboard test.<sup>25</sup> Similarly, a series of 50 children with well-controlled epilepsy on CBZ monotherapy showed better motor steadiness and attention span in the peak CBZ saliva level.<sup>26</sup> Therefore, although CBZ might negatively impact cognition, it might improve some motor components, especially when it substitutes more sedating AEDs.

Compared with other AEDs, CBZ has a better profile in some components and worse in others. A study of 64 children with new onset epilepsy and no neurological deficit randomized patients to CBZ, phenytoin (PHT) or sodium valproate (VPA). After 6 months of treatment, memory scores (recent recall) were worse for children on CBZ than those on VPA, and vigilance and concentration had no significant differences. After 1 year of treatment reading scores were lower in the CBZ group than in the PHT group.<sup>27</sup> Patients on CBZ had increased irritability, nervousness and disturbed sleep at the one month evaluation, but these were not present at 6 months.<sup>28</sup> Another study evaluated 33 children receiving phenobarbital (PB) or CBZ with focal or secondarily generalized seizures at intake and at 6 and 12 months and found no significant changes over time regarding behavioral or cognitive effects with either AED.<sup>29</sup> Another group found no significant differences regarding seizure control or adverse effects in a multicenter study with 260 children with newly diagnosed epilepsy receiving either CBZ or VPA.<sup>30</sup> Finally, a series of 67 children with newly diagnosed focal epilepsy and normal baseline intelligence randomized patients to CBZ or LTG and found improved performance IQ and unchanged behavioral scores in both groups.<sup>23</sup> However, the parental Conners scale improved in the CBZ group when compared to the LTG group.

Even though there are multiple studies regarding the adverse neurological effects of CBZ in children they are extremely heterogeneous and difficult to compare. CBZ has a better

cognitive and behavioral profile compared to classic AEDs (PB and PHT) and there are no severe cognitive or behavioral impairment caused by CBZ, with most deficits related to memory.

## Clobazam

Clobazam (CLB) has nitrogen radicals in positions 1 and 5, rather than in positions 1 and 4 as other benzodiazepines (BZD). CLB binds to the  $\gamma$ -aminobutyric acid (GABA)<sub>A</sub> receptor increasing GABA transport and glutamate reuptake.<sup>31,32</sup> It is a broad spectrum AED, effective in focal seizures, focal seizures with secondarily generalization, drop attacks, status epilepticus, febrile seizures, and in Lennox-Gastaut syndrome.<sup>33-41</sup>

Sedation is a common side effect of CLB and it often interferes with daily function.<sup>19,42,43</sup> A study of 300 children with refractory epilepsy in whom CLB was added to the treatment regimen found adverse effects in 25%. They included tiredness, sleep problems, and mood or behavioral changes, but 78% of these were considered minor and did not result in discontinuation.<sup>42</sup> When CLB was added to children with intractable epilepsy side effects such as excessive sedation, irritability, and behavioral changes were present in 22.5%, but some were transient and responded to dose reduction.<sup>43</sup> In a series of 115 children with refractory epilepsy, CLB as an add-on AED resulted in improvement in neurological functions (mainly alertness) in 72%, although 26% described worsening in at least 1 neurological function. The improvement in neurological functions (balance, mood, alertness, and attention) was observed more frequently when a 1,4 BZD taken at baseline was discontinued<sup>44</sup> and, therefore, can be partially attributed to substitution of a BZD with more neurological adverse effects rather than to the primary effect of CLB. Of 63 children with refractory epilepsy in which CLB was administered aggression, hyperactivity, insomnia, depression, and suicidal ideation were among the side effects.<sup>45</sup> Finally, when CLB was added to 36 children with intractable epilepsy it was better tolerated than other BZDs.<sup>46</sup> Nonetheless, unfavorable side effects were present in 47%, including drowsiness, mild ataxia, salivation, and fatigue, but they were mild, transient and most decreased on the same dose so withdrawal was not needed.<sup>46</sup> Favorable effects on alertness or behavior were present in only 2 patients (5%).<sup>46</sup>

When compared with other AEDs, a multicenter study in 253 epileptic children treated with CLB, CBZ or PHT in monotherapy, found no difference in effectiveness.<sup>47</sup> CLB induced slightly more behavioral effects and tolerance developed in 7, 5% whereas only in 4, 2% with CBZ and 6, 7% with PHT.<sup>47</sup> Another study with a subset of the aforementioned population of children found no differences between CLB, CBZ, and PHT in any of the assessed neuropsychological measures (memory, attention, psychomotor speed, and impulsivity) in the initial 1-year follow-up assessments.<sup>40</sup> In this series, there were no differences in internalizing and externalizing behaviors with PHT, CBZ, and CLB.<sup>40</sup> A study of 45 children with epilepsy with centrotemporal spikes found that children on CLB had less cognitive and behavioral adverse effects than children on CBZ.<sup>34</sup>

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