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Cognitive Side Effects of Antiepileptic Drugs in Children

By David W. Loring, Ph.D., Psychiatric Times
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Epilepsy is a major public health concern, with prevalence estimated to be slightly less than 1% (Annegers, 1996). Each year, 25,000 to 40,000 children in the United States alone experience their first unprovoked seizure (Hirtz et al., 2003). Depending on the type of seizure (e.g., generalized versus focal) or specific epilepsy syndrome (e.g., juvenile myoclonic epilepsy, benign rolandic epilepsy), there are several recommended medications with demonstrated clinical efficacy from which to choose (Hirtz et al., 2003). Selection of a specific medication, however, is often based upon clinical experience due to the absence of adequate antiepileptic drug (AED) pediatric clinical trials.

Antiepileptic drugs decrease membrane excitability, increase postsynaptic inhibition or alter synchronization of neural networks to decrease excessive neuronal excitability associated with seizure development. Common side effects of decreasing neuronal excitability, however, are slowed motor and psychomotor speed, poorer attention and mild memory impairment (Meador, 2005). Unlike adults, cognitive side effects in children occur against the backdrop of normal cognitive and psychosocial development, and treatment decisions made in childhood may have lifelong implications. Adults who developed epilepsy during their childhood tend to have less education, decreased rates of employment and employment at lower job levels, lower rates of marriage, poorer physical health, and increased incidence of psychiatric disorders (Jalava and Sillanpaa 1997a, 1997b; Jalava et al., 1997; Sillanpaa et al., 1998). Importantly, these long-term effects are also present in adults who are no longer taking medications. The persistence of these effects after discontinuation of AED treatment suggests a role of either seizure etiology, cumulative effects of repeated seizures or AED treatment permanently altering the course of development. Because significant brain impairment and more frequent seizures are associated with more difficult-to-treat epilepsy, these patients are unlikely to stop their seizure medications. Studies in rats have shown significant AED effects in the developing brain including apoptotic neurodegeneration (Bittigau et al., 2003; Olney et al., 2002). Thus, long-term AED side effects should be considered when selecting an AED for pediatric use.

Cognitive AED side effects in children, unfortunately, have been inadequately studied (Loring and Meador, 2004). Although several patterns of AED treatment in young adults continue to be described, the lack of data needed to generate evidence-based AED guidelines in children has been highlighted by the American Academy of Neurology (AAN), Child Neurology Society (CNS) and American Academy of Pediatrics (AAP) (AAP Committee on Drugs, 1995; Hirtz et al., 2003). A recent AAN/CNS practice guideline stated, "Behavioral and cognitive side effects

need to be better evaluated, especially for new AED[s], and individual risks as well as group differences assessed on tests of cognition" (Hirtz et al., 2003). The AAP Committee on Drugs (1995) concluded, "Few studies have been comprehensive, and for most drugs, neuropsychological effects have been incompletely described." Thus, major organizations representing both pediatrics and neurology emphasized the need to establish the neuropsychological profiles of newer AEDs in children and to determine the behavioral and cognitive consequences of long-term AED treatment on academic achievement and neuropsychological function to maximize treatment effectiveness.

Phenobarbital (Luminal, Solfoton) and traditional benzodiazepines are associated with the greatest risk of cognitive side effects. The effects of phenobarbital are well established since it was used for many years for seizure prophylaxis after a febrile seizure. Although no longer a first-line therapy, its effects on IQ illustrate a pattern for concern that requires careful examination in all AEDs with demonstrated cognitive side effects. In studies, children on phenobarbital displayed IQ declines (Farwell et al., 1990; Wolf et al., 1981), and although IQ improved following discontinuation of phenobarbital (Farwell et al., 1990; Sulzbacher et al., 1999), there continued to be long-term achievement effects when these children were tested three to five years later (Sulzbacher et al., 1999). The inability of children to fully catch up and compensate for "lost time" is important because it suggests a more complex interaction of AED therapy and developmental maturation than simply interfering with new learning efficiency. Because IQ declines are thought to reflect slowed mental growth rather than a loss of previously acquired cognitive function or cognitive regression, concern exists that any AED with cognitive side effects may result in significant impairment based upon cumulative effects if used over extended periods.

The cognitive side effects of carbamazepine (Equetro, Tegretol), phenytoin (Dilantin) and valproate sodium (Depacon) are comparable and associated with modest psychomotor slowing accompanied by decreased attention and memory (Meador, 2005). Neuropsychological side effects generally emerge according to a dose-dependent relationship (Meador, 2005); however, both quality of life (Gilliam, 2002) and memory may be affected, even when serum blood concentrations are within standard therapeutic ranges. In children, AED effects are seen in decreased performance on the Continuous Performance Test (CPT) (Mandelbaum et al., 2003) or memory. In addition, some children are at heightened risk for developing disproportionate cognitive side effects with carbamazepine (Seidel and Mitchell, 1999). Treatment with carbamazepine has also been associated with electroencephalogram slowing in the alpha range (Frost et al., 1995). How these short-term effects translate into academic achievement has not been adequately established (Bailet and Turk, 2000). However, there appears to be some relationship between the magnitude of EEG slowing and subsequent decline on selected Wechsler Intelligence Scale for Children-Revised (WISC-R) subtests tested after one year of therapy (Frost et al., 1995).

Newer AEDs

With the exception of clobazam, which is not approved for use in the United States, there are virtually no formal neuropsychological investigations of the recently introduced AEDs in children. Children on clobazam have similar neuropsychological profiles to those on carbamazepine or phenytoin after one year of treatment, with the exception of one test measuring psychomotor processing speed (WISC-R Coding). Practice effects were also present for many neuropsychological measures, and without an appropriate control group, the magnitude of cognitive side effects

cannot be determined because negative cognitive effects associated with AED treatment may be offset by performance improvement from repeated test exposure.

Felbamate (Felbatol) was the first of the new generation AEDs to be introduced to the U.S. market, but the development of idiosyncratic aplastic anemia and hepatotoxicity has markedly limited its use. Gabapentin (Neurontin) soon followed, and, in studies of young adults, it has repeatedly been associated with good neuropsychological profiles with little or no cognitive impairment (Leach et al., 1997; Martin et al., 1999; Meador et al., 1999). Gabapentin appears to decrease peak alpha frequency of the EEG, however, even in the absence of a cognitive effect (Salinsky et al., 2002). The clinical significance of this EEG effect is not known, although it demonstrates a gabapentin effect directly on the central nervous system, which raises the possibility that long-term treatment in children may be associated with some degree of cumulative cognitive side effects. The amount of EEG slowing with gabapentin is less than that seen with carbamazepine and, as already discussed, EEG slowing in children with epilepsy being treated with carbamazepine may be related to later IQ subtest performance.

Lamotrigine (Lamictal) is also associated with little or no objective cognitive impairment (Martin et al., 1999; Meador et al., 2005, 2001). Because of its positive psychotropic effects, lamotrigine has been used in treating bipolar disorder. However, it is important to recognize that mood as a moderator variable is a subjective report of cognitive functioning. In multiple reports, there is a discrepancy between self-reports of cognitive functioning and objective neuropsychological performance. There is little direct correlation between objective and subjective findings, although a robust relationship between subjective ratings of cognitive performance and mood is consistently reported (Salinsky et al., 2002). Thus, patient self-reports of improved cognition must be interpreted cautiously, even when mood is statistically controlled (Khan et al., 2004). Improved alertness may be seen with lamotrigine, even in patients with severe epilepsy syndromes, including tuberous sclerosis (Franz et al., 2001). Parents rated children as improved, with a longer attention span and improved alertness, in slightly more than half of one group sample of children with epilepsy who began lamotrigine therapy (Uvebrant and Bauziene, 1994). However, open-label studies using ratings are subject to the criticism of being confounded by expectations on the part of the nonblinded rater.

Levetiracetam (Keppra), which has been associated with some reports of irritability and aggression, appears to have a favorable cognitive side-effect profile. In an open-label study in autism, levetiracetam had beneficial effects on attention, hyperactivity and mood instability (Rugino and Samsock, 2002). It has been associated with nonsignificant increases in reaction time, but the size of reaction time slowing for levetiracetam was smaller than for oxcarbazepine (Trileptal) and carbamazepine. Unlike these other two AEDs, levetiracetam was not associated with a change in any EEG or visual evoked potential parameter (Mecarelli et al., 2004).

Oxcarbazepine is structurally similar to carbamazepine, but appears to have a better cognitive profile. It has been associated with both neuropsychological impairment and EEG slowing in healthy volunteers (Salinsky et al., 2004), although the magnitude of effect appears to be smaller than with carbamazepine (Mecarelli et al., 2004). Again, the long-term significance of slight EEG slowing, if any, has not been established.

There is little information about tiagabine (Gabitril) and vigabatrin. Very little formal cognitive data about tiagabine exist, although any cognitive effects appear modest (Dodrill et al., 1998). In one small add-on study, tiagabine was associated with a decline in verbal memory as well as less energy (Fritz et al., 2005). Vigabatrin has not been approved for use in the United States due to risk of visual field constriction, although its cognitive profile is reportedly good (Provinciali et al., 1996).

The greatest concern of cognitive side effects in the new generation of AEDs is seen with topiramate (Topamax) (Martin et al., 1999; Meador et al., 2005; Salinsky et al., 2005; Thompson et al., 2000) and, to a smaller degree, zonisamide (Zonegran) (Akaho, 1996; Berent et al., 1987). Little formal study of the cognitive side effects of zonisamide has been done, but there have been both clinical trials and clinical reports indicating concern for topiramate.

Topiramate has an approvable letter from the U.S. Food and Drug Administration for pediatric use, although there is evidence from many sources that at certain doses there is a risk of neuropsychological impairment (Dooley et al., 1999; Kockelmann et al., 2003; Meador et al., 2003; Salinsky et al., 2005). The possibility that some patients may be at heightened risk for cognitive impairment with topiramate remains a possibility (Meador et al., 2003). Although worse than those of most newer AEDs, the cognitive side effects of topiramate are generally comparable to those associated with valproate sodium (Meador et al., 2003). These adult studies have been conducted using doses and escalation schedules that are higher and faster than those used in current practice. Whether these deficits are present at lower doses is not presently known, and there has been a recent trend for lower dose use.

Conclusions

There are many methodological limitations in the literature of AED effects in children using older treatment options that have prevented firm conclusions from being drawn, and many older studies have relied solely on IQ, which tends to be an insensitive measure to all but the most significant neuropsychological impairment (Lezak et al., 2004). In addition, no comparative randomized, controlled trials have been conducted in children using newer AEDs available in the United States. The most recent generation of AEDs tend to have more favorable cognitive profiles than older treatment options, although even newer AEDs with little or no consistent neuropsychological side effects may not be completely benign cognitively. Whether relatively small cognitive effects result in cumulative neuropsychological difficulty or decreased academic performance in children has not been properly investigated and is largely unknown. There is a critical need for appropriate prospective long-term studies of AEDs and cognitions in different applications to determine which drugs and which factors may affect school performance and social adjustment during the school years. Treating children with AEDs associated with better neuropsychological outcomes will maximize school performance, decrease the need for special services in school, and increase quality of life for both patients and their families.

Dr. Loring is professor in the departments of neurology and clinical health psychology at the University of Florida.

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