

# Behavioral and Cognitive Effects of Anticonvulsant Therapy

Committee on Drugs

In 1985, the Committee on Drugs reviewed evidence, primarily from adult studies, indicating that anticonvulsant therapy may have detrimental effects on behavior and cognition.<sup>1</sup> It was recommended that pediatricians judiciously review indications for the use of antiepileptic medications, weigh the efficacy versus the side effects of specific drugs, and be alert to reported changes in patient behavior, mood, or cognitive function. Furthermore, the Committee noted the need for the development of brief neuropsychologic screening tests to identify subtle intellectual and behavioral side effects as well as the need for the delineation of behavioral and cognitive effects of specific antiepileptic medications in children.

This commentary presents an overview of current pediatric studies of antiepileptic drugs and cognitive/behavioral function.

## Behavioral Effects

Behavioral disturbances, reported in 20% to 30% of children with epilepsy,<sup>2</sup> are frequently unrelated to the anticonvulsant drug regimen, but may result from disordered cerebral function or occur as a secondary reaction to the illness.<sup>3</sup> Some children with seizures differ behaviorally from healthy controls both before the initiation of treatment and after its cessation. Behavioral differences are most prominent with absence and partial seizures.<sup>4</sup>

The most comprehensive incidence data on the behavioral side effects of antiepileptic drugs derive from a study of 392 children receiving long-term monotherapy with phenobarbital, primidone, phenytoin, carbamazepine, or valproate for treatment of epilepsy or febrile convulsions.<sup>5</sup> As shown in the Table, behavioral effects were most commonly reported in patients treated with phenobarbital, and were relatively uncommon in children treated with primidone, phenytoin, or valproate. Drowsiness and longer sleep were associated with higher plasma levels of phenobarbital, whereas signs of excitation tended to occur at lower dosages and resolved when higher or stable plasma levels were achieved. Although the behavioral side effects of phenobarbital were considered intolerable in 20% of patients, withdrawal of medication was necessary only in the 4% whose symptoms failed to resolve with a change (increase or decrease) in dosage. In a smaller study, phe-

nobarbital was discontinued in 14% of 28 children because of severe behavioral problems<sup>6</sup>; these effects, however, are commonly transient and may be clinically undetectable after 1 to 2 months of treatment.<sup>6,7</sup>

The common behavioral effects of carbamazepine were either positive (improved mood) or related to drowsiness and impaired sleep.<sup>5</sup> In a prospective study of the psychological effects of valproic acid and carbamazepine in 63 newly diagnosed epileptic children, no notable behavioral effects were evident 12 months after the initiation of treatment.<sup>4</sup> This study did not assess sleep or drowsiness.

A study of the prevalence of psychopathology in 39 children with epilepsy evaluated by psychiatric interview suggested a high rate of major depressive disorder following the initiation of phenobarbital therapy in children with a family history of affective disorder.<sup>8</sup> The authors noted that depressive disorder may be overlooked unless the assessment includes an interview of the child, because considerable overlap exists between common behavioral side effects (irritability, sleep difficulty, or inattention) and the symptoms of childhood depression. Depression that resolves with discontinuation of therapy has also been reported in adolescents treated with primidone, of which phenobarbital is a metabolite.<sup>9</sup>

## Cognitive Function in Children With Epilepsy

Several studies have explored predictors of neuropsychologic function and academic achievement in children with epilepsy.<sup>10-12</sup> Significant lowering of cognitive potential and increased neuropsychologic impairment were found in children with epilepsy when compared with age-matched controls.<sup>10</sup> IQ and academic achievement were related to age at onset of seizures, duration of seizure disorder, and type of seizure. All subjects with minor motor or atypical absence seizures showed some degree of neuropsychologic impairment, and most required special education or had experienced failure in school.

Uncontrolled studies of schoolchildren with epilepsy reported rates of academic underachievement ranging from 16% to 50% in general knowledge, arithmetic, and spelling.<sup>11,12</sup> Treatment variables (number of anticonvulsants or duration of treatment) were not significant predictors of underachievement.

## Cognitive Effects of Anticonvulsant Drugs

Although several of the antiepileptic drugs have been shown to affect specific functions such as attention, concentration, memory, and motor speed, a recent study suggested more global depression of cognitive function in children receiving long-term

The recommendations in this statement do not indicate an exclusive course of treatment or procedure to be followed. Variations, taking into account individual circumstances, may be appropriate.

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**TABLE.** Percentage of Patients on Monotherapy Reporting Behavioral Effects\*

	Phenobarbital (n = 99)	Primidone (n = 85)	Phenytoin (n = 63)	Carbamazepine (n = 35)	Valproate (n = 110)
Behavioral effects	61	22	16	31	17
Irritability	24	8	6	6	5
Restless and short sleep	24	4	6	9	4
Hyperactivity	22	8	3	3	5
Better and longer sleep	12	2	2	3	5
Drowsiness	7	5	2	11	5
Better mood		1		9	

\* Adapted from Herranz et al.<sup>5</sup>

phenobarbital treatment. Two hundred seventeen children with febrile seizures randomly assigned to phenobarbital or placebo treatment for a 2-year period were evaluated 2 years after the initiation of treatment and again 6 months later.<sup>9</sup> Although the mean IQ of the phenobarbital group was significantly lower than that of the placebo group (7 points at 2 years, 4.3 points at 2½ years), factors such as noncompliance and a 30% rate of crossover in the placebo group act to obfuscate the importance of the findings. Long-term phenobarbital maintenance was also investigated by comparing the IQ of schoolchildren 6 months or more after the initiation of treatment and again 9 to 12 months later. Similar testing was performed for nonepileptic controls and children receiving valproic acid. Although all groups had numerically higher IQ scores on retesting, the improvement was not statistically significant for the group receiving phenobarbital.<sup>13</sup>

A well-designed crossover study of neuropsychologic function in 21 school-age children receiving therapeutic levels of phenobarbital or valproic acid for 6-month periods showed modest improvement in performance with use of valproic acid; statistically significant differences were seen for four of 24 measures (block design, performance IQ, full scale IQ, and Berkeley Paired Association Learning Task).<sup>6</sup>

Valproic acid and carbamazepine have little measurable effect on cognitive performance when used as monotherapy at therapeutic levels.<sup>14</sup> In England, 63 schoolchildren with newly diagnosed epilepsy who were cared for by a general pediatrician (ie, uncomplicated cases) were evaluated before treatment with carbamazepine or valproic acid and at intervals during a 12-month period.<sup>4</sup> No decline was seen on measures of school attainment or intelligence, although both drugs had transient negative effects on measures of attention. A Swedish longitudinal study assessed measures of speed, information processing and attention, and memory function in 100 school children who had been free of seizures while receiving monotherapy (carbamazepine, valproic acid, or phenytoin) for at least 1 year.<sup>15</sup> Retesting after drug withdrawal showed improvement on only one of 12 test measures (fingertapping with the dominant hand), suggesting that these anticonvulsant drugs did not adversely affect neuropsychologic function.

Adverse cognitive effects of anticonvulsant drugs are commonly dose-related. Reanalysis of data from a study comparing cognitive function in epileptic adults treated with phenytoin and car-

bamazepine found that the relative impairment on measures of cognitive function initially described in the phenytoin group disappeared when subjects with high phenytoin levels were excluded.<sup>16</sup> A study of drug effects conducted in a special school for children with complex seizure disorders, learning problems, and psychiatric disorders reported significant deterioration on repeated intelligence testing in 16% of subjects.<sup>17</sup> High blood levels of anticonvulsant drugs (phenytoin, phenobarbital, or primidone) were significantly related to cognitive decline. Higher serum levels of carbamazepine and valproic acid are also associated with impairment in adults, despite the minimal effect on higher cognitive function at therapeutic levels.<sup>14</sup> In contrast, carbamazepine use has been associated with dose-dependent improvement on measures of reaction time, attention, and impulsivity.<sup>18</sup>

Polytherapy in children with seizures has not been well studied. In adults, a body of literature reflects improved performance, usually without compromising seizure control, with a reduction in the number of anticonvulsant drugs.<sup>14</sup>

#### Screening for Cognitive and Behavioral Side Effects

With few exceptions, such as the clinical hyperactivity reported in a small percentage of patients treated with phenobarbital, cognitive and behavioral side effects of anticonvulsant drugs are subtle and may be discrete, affecting isolated functions rather than overall performance. The effects of drugs on cognitive function have been defined through the use of neuropsychological tests that encompass a broad spectrum of functions related to learning, including motor speed and dexterity, attention, memory, and processing. However, few studies have been comprehensive, and for most drugs, neuropsychological effects have been incompletely described. The diversity and subtlety of the side effects, combined with our limited knowledge of drug-specific effects, preclude the development of practical and effective in-office screening procedures. Children with persistent difficulty despite adjustment of medication warrant careful evaluation. Behavioral concerns may be addressed by the pediatrician, clinical psychologist, or school counselor. Academic difficulty in a child with seizures signals the need for evaluation of intellectual potential and language/learning ability. Such testing is available through the public schools upon request by the family or physician, or may be obtained through practicing psychologists, speech pathologists, or educational diagnosticians. The test

battery should include standard intelligence tests (the McCarthy Scales of Children's Abilities or Stanford-Binet for preschool and the Wechsler Intelligence Scale for Children or Stanford-Binet for school-age children), and achievement tests such as the Wide Range Achievement Test or Woodcock-Johnson.

### RECOMMENDATIONS

In view of the potential for antiepileptic drugs to adversely affect cognition and behavior in a population already at risk for disability, the Academy makes the following recommendations:

1. Physicians prescribing anticonvulsants should have an understanding of the natural history of seizure disorders, especially knowledge regarding when to initiate medications and when to discontinue them.
2. When an anticonvulsant medication is required, the physician must consider the specificity of the drug for the seizure type, as well as the drug's potential side effects. Thus, the relative influence of each anticonvulsant agent on behavioral and cognitive functions should be considered, along with all other potential adverse effects.
3. If anticonvulsant therapy is initiated, the physician should monitor the child's behavior and academic progress through routine questioning of parents (and teachers when relevant) and observation of cognitive function, mood, and behavior during follow-up visits.
4. If changes in the child's behavior or cognitive performance occur in relation to the initiation of anticonvulsant therapy, the need for medication and/or possible alteration of medication must be reassessed.
5. If school problems persist, the physician should advocate a comprehensive evaluation of cognitive potential and learning ability in order to plan for appropriate remediation or intervention.

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*Pediatrics* 1995;96;538

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*Pediatrics* 1995;96;538

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