Cognitive Effects of “Older” Anticonvulsants in Children with Epilepsy: A Review and Critique of the Literature

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Cognitive decline in children with seizure disorders is due to several factors, one being the choice of anticonvulsant and total anticonvulsant exposure. This paper reviews research investigating cognitive effects associated with “older” anticonvulsant medications (i.e., phenobarbital, phenytoin, carbamazepine, and valproate) prescribed as monotherapy. A number of cognitive difficulties such as intellectual decline, mild memory loss, visual-motor impairment, and psychomotor slowing have been associated with these medications. Each study included in this review is assessed in terms of the appropriateness of study design and ability of the reader to draw clear conclusions about the cognitive effects associated with the anticonvulsant under investigation. The review also includes a synopsis of the myriad of methodological difficulties that plague this body of literature. Conclusions that can be drawn from the existing literature are delineated, and future directions for research are suggested.

Keywords: phenobarbital, valproate, carbamazepine, phenytoin, anticonvulsant, antiepileptic, epilepsy, cognitive effects

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INTRODUCTION

Seizure disorders have been associated with cognitive decline in children. However, there does not appear to be one profile of neuropsychological scores that is characteristic of children with epilepsy. Instead, children with epilepsy demonstrate a wide range of abilities on various cognitive tasks. A list of commonly used cognitive tasks and the areas of cognition they measure can be found in Table 1. The degree of impairment or lack thereof in children with epilepsy has been shown to be mediated by numerous factors, including age of onset,^{1,2} seizure type,¹ duration of the seizure disorder,¹ the presence versus absence of visible underlying pathology,³ responsiveness of seizure activity to treatment,^{2,4} and the choice and amount of pharmacologic treatment used.^{1,5} Because of the multitude of factors thought to contribute to cognitive decline of children with seizure disorders, it is often dif-

ficult to systematically investigate the effects of one factor while controlling for other variables. This is especially true because several of the factors are highly correlated with one another. For example, age of onset is highly correlated with the duration of the seizure disorder. Additionally, most of these factors cannot be manipulated experimentally in human studies. Hence, it is often difficult to draw strong conclusions about the degree to which each factor contributes to cognitive impairment. One group of variables that can be and has been manipulated experimentally is those factors that relate to the pharmacological treatment of epilepsy (i.e., choice and duration of pharmacological therapy). Therefore, it is ostensibly possible to gain a clear picture of the cognitive effects of anticonvulsants from well-designed clinical trials.

This paper provides a comprehensive review and critique of the literature relating to cognitive effects of four “older” anticonvulsants: phenobarbital, carbamazepine, valproate, and phenytoin. A review of this information is critical because these medications are widely prescribed for the treatment of epilepsy and are typically the primary or sole agent used for this pur-

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pose. Knowledge regarding the cognitive effects of these medications allows practitioners and parents to make informed decisions regarding which anticonvulsant should be prescribed.

The objectives of this review are four-fold. The first section of this paper will provide a general overview of the cognitive effects of seizure disorders that are *not* related to anticonvulsant monotherapy. This section is not intended to be an exhaustive review of the epilepsy literature on pediatric cognition, but instead is included to emphasize the fact that the cognitive performance of children with seizure disorders is affected by a multitude of factors other than medications. These factors are also critical to this review because they may influence the choice of anticonvulsant and are important to consider when evaluating the medical literature. The second objective will be to review the various techniques used by researchers to conduct well-controlled investigations of the effects of this class of drugs. Third, research about the cognitive effects of the four "older" anticonvulsants that are frequently used as monotherapy will be reviewed and critiqued. Although polytherapy increases the risk for toxicity, drug interactions, and exacerbation of seizures in some patients,⁶ this review will be limited to studies examining their effects in monotherapy. There is also evidence that polytherapy has a greater negative impact on cognitive functions than does monotherapy. Finally, a general methodological section will comment on the overall degree to which the existing literature has been successful in clearly delineating the effects of anticonvulsants on cognition. Conclusions regarding the effect of these medications on pediatric cognitive functioning will be drawn, and future directions for research in this area will be suggested.

COGNITIVE IMPAIRMENT RELATED TO SEIZURE DISORDERS

Research has indicated that while some children with seizure disorders do not demonstrate cognitive impairment, many children with ongoing seizure activity do have decreased academic performance compared to "normal" children and perform more poorly on tests of neurocognitive functioning.^{2,3} The great variability in the academic achievement and neuropsychological

functioning of children with epilepsy relates to many factors, including seizure type, severity and frequency of seizures, level of control of the seizures achieved through treatment, age of onset, and the effect of anticonvulsant medications.

It is well established that various seizure types and syndromes are associated with different profiles of cognitive impairment in children.⁷ Seizure disorders of greater severity and more extensive brain pathology are assumed to underlie the disorders that are often associated with more extensive cognitive impairment. Seizure activity of a severe nature, such as refractory symptomatic status epilepticus, is often associated with profound cognitive impairment and mental retardation.⁸ Epileptic syndromes characterized by severe, intractable seizure activity such as Lennox Gastaut Syndrome are also associated with a high risk of cognitive decline.^{9,10} In contrast, children that experience simple febrile seizures, benign Rolandic epilepsy, juvenile myoclonic epilepsy, and childhood and juvenile absence epilepsy generally have normal intellectual functioning.⁸ As stated before, a wide variety of cognitive profiles are found in children with epilepsy. The observed profiles of cognitive impairment in children with partial onset seizures are greatly influenced by the locus of seizure activity. For example, seizure activity originating in the temporal regions generally predicts impairment in cognitive abilities associated with functioning of this brain area such as memory consolidation.¹¹

Effectiveness of treatment in controlling seizures is also related to cognitive outcome in children. Intellectual performance appears to decline over time in children with uncontrolled seizures; however, no change in IQ is found in children whose seizures have remitted.^{2,4} Other research indicates that seizure frequency is directly correlated with IQ performance, but it is not related to the children's placement in mainstream versus non-mainstream classes.¹ Higher levels of attention and memory performance have also been associated with the lack of seizures in the year before testing.⁵

Several investigators have related early onset of seizure activity to poorer academic and neuropsychological prognosis, although support for this proposition is not well documented. Research indicates that age of onset is directly

related to IQ and to the probability of remaining in mainstream schools.^{1,2} Bourgeois et al. also found evidence for an association between early age of seizure onset and lower IQ.¹² Using discriminant analysis, early age of onset and number of supratherapeutic anticonvulsant concentrations correctly classified 71% of children in the following groups: IQ remained the same from initial to last testing; IQ increased by 10 points, or IQ decreased by 10 points. Early age of seizure onset has also been associated with poor performance on measures of attention and

memory.⁵ In contrast to the above findings, Bailet and colleagues did not find any significant relationship between age of onset and neurocognitive performance.¹³ This discrepancy may relate to the select population of children with epilepsy targeted by these authors. The sample of children in this study was limited to those with IQ above 80 that exhibited no abnormal findings on computed tomography (CT) or magnetic resonance imaging (MRI) scans. It may be that earlier age of seizure onset is related to exacerbated cognitive difficulties in most chil-

Table 1. Common Neurocognitive Measures Used in Anticonvulsant Studies

AREA OF NEUROCOGNITIVE FUNCTIONING USING STANDARDIZED TEST	TEST DESCRIPTION
INTELLIGENCE AND ACHIEVEMENT	
Wechsler Adult Intelligence Scale (WAIS-R, WAIS-III) Wechsler Intelligence Scale for Children (WISC-III) Wechsler Preschool and Primary Scale of Intelligence (WPPSI) Stanford-Binet Intelligence Test Detroit Tests of Learning Aptitude	Three main composite scores: Full, Verbal, and Performance Scale scores. Full Scale IQ relates to general intelligence, academic aptitude. Verbal Scale IQ reflects verbal comprehension and language processing. Performance IQ measures perceptual organization and the ability to manipulate and use visual images. The Composite Score provides a global estimate of cognitive ability. Intelligence test that yields an Overall Aptitude Composite by Test assessing four subsets of mental functioning termed the (i.e., Linguistic, Cognitive, Attentional, and Motoric Domains).
McCarthy Scales of Children's Abilities	Measure of cognition ve ability that yields a General Cognitive Index (GCI). Five additional scales include: (i.e., Verbal Scale, Perceptual-Performance Scale, Quantitative Scale, Memory Scale, and Motor Scale)
Bayley Scales of Infant Development	Mental Developmental Index provides an estimates of early cognitive development.
Wide Range Achievement Test (WRAT-R)	Brief achievement test with three subtests: Reading, Spelling, and Arithmetic.
Peabody Individual Achievement Test (PIAT)	Achievement test that assessing mathematics, reading recognition, reading comprehension, spelling and general information.
Raven's Progressive Matrices	Nonverbal test of reasoning ability
Porteus Maze	Nonverbal test of performance in intelligence
MEMORY	
Wide Range Assessment of Memory and Learning (WRAML)	Tests verbal and visual memory and Also assesses one's rate of learning information over several trials.; measures immediate and delayed recall Immediate and delayed recall can be measured.
Paired Associates	Assesses one's rate of learning verbal information; measures immediate and delayed recall
LANGUAGE	
Boston Naming Test	Measures of word retrieval and object naming from line drawings
Neale Reading Test	Measures reading accuracy, comprehension and speed
ATTENTION	
Stroop Color and Word Test	Test of mental control and impulsivity. A list of color names is read in which no name is printed in its matching color.
Matching Familiar Figures Test	Match-to sample test in which a picture is matched with an identical picture from among an array of six similar images
Trails B	Measure of speed of visual search, mental flexibility, attention, and motor function
Continuous Performance Task (CPT)	Computerized test of sustained attention, vigilance, and impulsivity
Cancellation Test	Measures of the accuracy of selective attention; and a tests of visual scanning and perception
Seashore Rhythm	Measures auditory attention, auditory discrimination, and short-term auditory sequential memory
VISUO-MOTOR PERCEPTION	
Bender Visual Motor Gestalt Test	Tests of perceptual-motor development
PSYCHOMOTOR SPEED, DEXTERITY	
Grooved Pegboard Test	Measures of psychomotor speed and dexterity
Finger Tapping Test	Test of psychomotor speed

* Description of test referenced from Sattler (1992)

** Description of test referenced from Adams, Parsons, Culbertson, and Nixon (1996)

Table 2: Phenobarbital and Phenytoin Studies

Reference (N)	Subject Characteristics	Design	Measures Used*	Findings
PHENOBARBITAL STUDIES				
15 (35 PB* 30 placebo)	mean age 15-17 mo; ≤1 febrile seizure; matched for gender, family history	BS†, PC‡, DB§, RA¶ Tested at 8 or 12 mo post-treatment	Bayley Mental or Stanford-Binet	No IQ difference between groups; PB performed worse on memory-concentration subscale of Stanford-Binet ; Correlation in PB group between serum PB concentration and memory-concentration performance
16 (25 PB* 25 placebo)	3-6 yrs at initial assessment; ≥1 febrile seizure; matched for gender, race, age, SES, no group difference in age at onset, duration of seizure, EEG	BS†, PC‡, DB§, RA¶ Withdraw study (tested 1-2 mo before cessation & 11-19 wks later)	WPPSI; Matching Familiar Figures and Children's Embedded Figures Test	No differences between groups at initial and follow-up assessment and in degree of change of test scores from initial to follow-up assessment
17 (217 PB* 150 placebo)	8-36 mo; ≥1 febrile seizure; no difference in age, sex, or SES	BS†, PC‡, DB§, RA¶ Initiation study with testing at baseline and 6 wks, 6, 12, 16, 24, and 36 mo	Bayley Mental at baseline, 6 wk, and sometimes 12 mo, Stanford-Binet at 2 and 2.5 yrs, sometimes at 12 mo	No difference in Bayley scores at 6 wks; Stanford-Binet scores significantly poorer in PB group (8.4 pts) at 2 yrs: at 2.5 yrs (~4 mo after treatment cessation), PB group still performed significantly worse on Stanford-Binet (5.2 pts) [#]
18 (53 PB* 51 placebo)	Follow-up to reference 17. 3-5 yrs later, after completion of 1 st grade	BS†	Stanford-Binet WRAT-R;	No difference in Stanford-Binet scores or in arithmetic or spelling subscores of WRAT-R; PB group performed worse on reading subtest of WRAT-R (11.7 pts) [#]
19 (9 PB*)	6-18 yrs; Various seizure types. Children treated with PB from 4-9.5 yrs, no EEG anomalies for 1 yr	Within-subject. Testing prior to and 6 mo after cessation	WISC; Benton Mult. Choice Test; 10 Luria words; Corsi Block Span Test; Cancellation tests; Trials A & B	After PB withdrawal: Significant PIQ improvement (8.6 pts) [#] , no significant VIQ or FSIQ improvement; Improvement on spatial STM (Benton test)**; Significantly faster times on "attention" tests (Cancellation)**; Improvement on visual-motor tasks (WISC Coding & Trails (A & B)) ; No significant improvement on verbal memory (Digit Span) or verbal and spatial learning (10 Luria words and Block SpanTest)
PHENYTOIN STUDIES				
24 (50 PHT)	4-14 yrs ; Most partial & generalized seizures, seizure-free for 2 mo	Within-subject. Testing at high and low salivary carbamazepine concentrations	Matching Familiar Figures; Aud-Vis Integrat. Test; STM task; CPT; seat mvmt maze task; graduated holes task; pursuit robr; Porteus maze	No consistent differences in cognitive functioning found at different concentrations

PB = phenobarbital; PHT = phenytoin

* = refer to Table 1 for description of neurocognitive measures; † BS = between-subject; ‡ PC = placebo controlled; § DB = double blind; ¶ RA = random assignment; || = No scores were reported to determine the clinical significance of results; # = "Points" reported refer to the difference in standard score performance between medication groups (for between subject design studies) or between test sessions (for within-subject design studies). Test scores used to calculate difference scores were either reported in the original study as standard scores with a mean of 100 and standard deviation of 15, or t-scores were converted to standard scores with a mean of 100 and standard deviation of 15 to allow comparison among study findings;***= Although these comparisons yielded statistically significant results, clinical significance of the results could not be evaluated because raw scores were reported instead of standard scores.

dren with epilepsy; however, the more subtle cognitive difficulties exhibited in children with very mild forms of epilepsy may not relate to age of seizure onset.

Additionally, the use of anticonvulsant polytherapy has been linked to poor academic and cognitive performance. Jayashree reported that children with epilepsy who received polytherapy performed significantly more poorly on tests of attention and memory than did epileptic children receiving monotherapy.⁵ Bulteau and colleagues also found that polytherapy (versus monotherapy or no therapy) was associated with lower IQ performance and placement in non-mainstream classes for children with "learning disabilities."¹ It is important to note that polytherapy is typically prescribed for children who have more severe and intractable seizures. Therefore, it is difficult to ascertain the degree to which cognitive impairment relates to the effects of polytherapy versus the effects of severe and intractable seizures in this study. Using a within-subject design, Ludgate et al. were able to focus more clearly on the deleterious effects of polytherapy by examining cognitive functioning of 18 adult patients with epilepsy before and one year after reducing the number of anticonvulsant's taken.¹³ Three patients withdrew from the study and resumed their pre-study dose of anticonvulsant therapy due to increased seizure frequency. In the remaining 12 subjects, reduction in polytherapy led to improved scores on Wechsler Adult Intelligence Scale (WAIS) performance IQ, visual retention performance, and a test of sustained attention. No change was noted on WAIS verbal IQ or verbal retention performance. These results indicate that anticonvulsant polytherapy has deleterious effects on pediatric cognition, and this impairment may be reversed with the reduction of polytherapy.

STUDY DESIGNS USED TO INVESTIGATE ANTICONVULSANT-ASSOCIATED COGNITIVE CHANGE

The plethora of variables affecting cognitive performance of children with epilepsy provides a challenge to investigators attempting to decipher the relative contribution of any one factor. This challenge of establishing the relative contribution of these factors in children is particu-

larly daunting because many of the factors influencing cognitive outcome are intrinsic to the study participants (thus, they are not able to be experimentally manipulated), and the factors are highly intercorrelated. Investigators have used different study designs in an attempt to isolate the cognitive effects in children that are due solely to anticonvulsant monotherapy. Different study designs used for this purpose include: anticonvulsant initiation and withdraw studies, between-subject placebo-controlled studies, dose-response studies, and comparison studies. In most anticonvulsant initiation and anticonvulsant withdraw studies, children with epilepsy serve as their own controls; however, some of these studies additionally use between-subject designs. In the typical anticonvulsant initiation study, children who have recently been diagnosed with epilepsy first receive baseline cognitive testing before the onset of pharmacotherapy and later undergo cognitive testing at one or more designated times following the initiation of anticonvulsant treatment. The cognitive effect of the anticonvulsant is assumed to be reflected in the difference score between performance before and after anticonvulsant treatment. In withdrawal studies, children receive cognitive testing before and after the cessation of an anticonvulsant. In most anticonvulsant withdraw studies, the anticonvulsant's effect on cognition is reflected in the amount of improvement shown in performance after cessation of treatment relative to performance while taking the anticonvulsant. A third study type employs a between-subject design in which the performance of children receiving anticonvulsant treatment is compared to a similar group receiving placebo. Anticonvulsant comparison studies constitute a type of between-subject study in which children are assigned to different medication groups to examine the relative amount of cognitive change caused by different anticonvulsants. In studies utilizing between-subject designs, random assignment to medication or placebo group and other forms of proper experimental and statistical control are critical to insure that groups do not differ on dimensions other than anticonvulsant treatment. Other study designs have focused on finding a dose-response relationship between anticonvulsant treatment and cognitive functioning. In these studies, children with epilepsy are first tested when drug concentration is

at the upper end of the reference range, and they are tested again when drug concentration is at the lower end of that range. If anticonvulsants have a concentration-dependent effect on cognitive functioning, there should be a statistically significant difference in performance at low and high anticonvulsant concentrations.'

COGNITIVE EFFECTS OF "OLDER" ANTICONVULSANTS USED AS MONOTHERAPIES

Phenobarbital

Of the four anticonvulsants chosen for review in this paper, phenobarbital has been available as an epilepsy treatment for the longest time. For this reason, much of the research examining the effect of a single medication on cognition has focused on the effects of this medication. The majority of studies examining the cognitive effects of phenobarbital exposure have involved infants and toddlers. Table 2 includes those studies evaluating the effect of phenobarbital.

A summary of studies evaluating the cognitive effects of phenobarbital is depicted in Table 2. Medication comparison studies that investigated phenobarbital are depicted in Table 3. A number of investigations have examined the cognitive effects of phenobarbital in toddlers who have experienced febrile seizures. Camfield et al. employed a double-blind, placebo-controlled study in which 65 toddlers who had experienced no more than one febrile seizure were randomly assigned to treatment or control groups.¹⁵ Cognitive assessment was conducted either 8 or 12 months subsequent to the onset of treatment. No significant difference in IQ was found between the treatment and control groups. There was a non-significant tendency for children receiving phenobarbital to perform more poorly than controls on the memory concentration subscore of the Stanford-Binet Test. A significant correlation was also found between serum drug concentration and memory concentration performance within the treatment group. Due to the well-controlled nature of this study and the large sample of children used, the finding of a nearly significant difference in memory performance would indicate a very mild memory problem in the children receiving phenobarbital. This study used highly appropriate experimental control techniques of randomization, blinding participants

and experimenters to the medication received by each child, and using placebo. Therefore, the conclusions can be clearly drawn about the short-term effects of phenobarbital in children who have had very mild seizure activity. However, these conclusions cannot be generalized to children who have more chronic phenobarbital exposure and/or more severe and/or chronic seizure activity.

An anticonvulsant withdraw study conducted by Wolf et al. also evaluated cognitive performance in 25 children receiving phenobarbital treatment after the occurrence of one or more febrile seizures.¹⁶ The average duration of phenobarbital therapy was 35 months. Children ranged from 3 to 6 years old at the initial assessment, which was performed just prior to treatment cessation. A follow-up assessment occurred 11 to 19 weeks after the children had their initial assessment. This study also used 25 case-matched control participants who had experienced febrile seizures but were not medicated. Assignment to medication group or control group was random, and the matching criteria included sex, race, age at time of testing, and socioeconomic status. No significant differences were found on intelligence, visual processing, or problem-solving measures between initial and follow-up testing within the treatment group or between the treatment and control groups. Therefore, the conclusion that phenobarbital therapy has little to no cognitive effect in children who have experienced very mild seizure activity is appropriate. These conclusions cannot be applied to children who have more severe or chronic seizure activity.

In contrast to the above reports, Farwell et al. found evidence for substantial effects of phenobarbital on cognitive functioning that persists for years after cessation of treatment.¹⁷ The 217 children ages 8 to 36 months involved in this double-blind, placebo-controlled study were randomly assigned to treatment or control groups. All children included in the study had experienced one or more febrile seizures. No significant difference in general intelligence was detected between the groups at 6 weeks after the onset of treatment. However, two years after the onset of treatment, children receiving phenobarbital performed an average of 8.4 points lower on the IQ measure than children receiving placebo. IQ was again assessed 6 months after the

cessation of phenobarbital treatment (2.5 years after treatment began). At this time, children who had been assigned to the phenobarbital treatment group performed an average of 5.2 points lower than controls. This research is the only well-designed study that investigates the cognitive effects of both brief and more chronic phenobarbital exposure in children who have experienced mild and transient seizure activity. The lack of cognitive side effects after brief phenobarbital therapy found in this study is congruent with the results of prior research. The results indicating the presence of mild, but persisting cognitive dysfunction associated with more chronic phenobarbital therapy is a useful extension of prior research.

Sulzbacher et al. conducted further assessment of 139 of the children who participated in the Farwell et al. study.¹⁸ Specific reasons for the high attrition rate in this follow-up study were not reported. The children were assessed 3 to 5 years after the original study. Children who had received phenobarbital treatment demonstrated significantly poorer reading performance than children who received placebo. No difference between groups was found for IQ or spelling or arithmetic performance. Because these authors were able to examine only a fraction of children first evaluated in the Farwell et al. study, it is difficult to ascertain whether the group of children assessed was representative of the children evaluated in the Farwell et al. report. Possible selective attrition of study participants calls the results of this study into question. Although this study may highlight long-term reading difficulties in children who had previously received chronic phenobarbital therapy, further research is clearly needed to assess the generalizability of this study's results.

An anticonvulsant withdraw study examined cognitive effects of phenobarbital in 9 children ages 6 to 16 years with various types of epilepsy who had been seizure-free for at least 2 years.¹⁹ The interval between pre- and post-cessation testing ranged from 6 months to over 4 years. A significant improvement in performance after phenobarbital cessation was found for performance IQ, visual-motor skill, and memory performance. The use of a within-subject design is a powerful tool for studying medication effects on cognition, and the cognitive improvements demonstrated after phenobarbital withdrawal

indicate that this anticonvulsant can have deleterious effects on cognition. Additionally, the finding of statistically significant results with such a small sample size indicates that the change in cognitive function is of substantial magnitude and/or is highly reliable.

A handful of studies evaluated the cognitive side effects of phenobarbital as compared to carbamazepine and valproate. A comparison study of the cognitive effects of carbamazepine or phenobarbital compared the performance of 33 newly diagnosed children randomly assigned to medication.²⁰ Intelligence testing was conducted within one week of enrollment in the study and subsequently at 6 and 12 months post-enrollment. Results revealed no significant difference in intellectual performance between the patients assigned to carbamazepine versus phenobarbital. The conclusion that phenobarbital and carbamazepine have comparable acute effects on intellectual performance can be drawn due to the random assignment of children to medication groups. No conclusions can be drawn about the cognitive effects of phenobarbital or carbamazepine relative to children not receiving medication.

Calandre et al. examined intellectual functioning in 64 school-aged children with epilepsy who were being treated with either phenobarbital or valproate monotherapy.²¹ Although seizure frequency was similar between the medication groups and participants were age-matched, random assignment to medication group was not employed. An initial assessment was conducted after the children had received over 6 months of pharmacotherapy, and a second assessment was conducted 9 to 12 months later. A control group of 60 neurologically normal children also received initial and follow-up assessments. At initial assessment, children receiving phenobarbital demonstrated lower verbal, performance, and full-scale IQ scores than controls, but the valproate group did not differ significantly from controls. At follow-up assessment, children receiving phenobarbital again demonstrated lower verbal and full-scale IQ performance than control subjects. The performance of children receiving valproate monotherapy did not differ from controls at initial or follow-up assessment. It was also noted that children in both the control group and the group receiving valproate, IQ scores increased significantly from initial to follow-up

assessment. This increase in performance was not seen in the phenobarbital group. It is difficult to determine the meaning of these results due to the choice of a neurologically normal control group and the lack of random assignment to medication.

A study using a double-blind, counterbalanced cross-over design presented a more extensive neuropsychological evaluation of the effects of phenobarbital and valproate.²² No placebo group was employed. The 21 children included in the study had tonic-clonic seizures, partial-complex seizures, or both. All seizure disorders were characterized by the authors as "mild." Phenobarbital treatment was associated with poorer performance and full-scale IQ and poorer verbal learning and memory than valproate treatment. Due to the well-constructed design employed in this study, the results appear to accurately reflect the relative cognitive effects of phenobarbital and valproate. Because of the lack of a control group, no conclusions can be drawn about the cognitive effects of either drug compared to placebo.

An anticonvulsant initiation comparison study randomly assigned 76 newly-diagnosed epileptic children to receive phenobarbital, carbamazepine, or valproate.²³ No control group was used. Intellectual functioning, Bender-Gestalt performance, and auditory event-related potentials were evaluated prior to anticonvulsant treatment onset and at 6 and 12 months after treatment onset. There was no significant difference in IQ or Bender-Gestalt scores among children who received different anticonvulsants. A slight but non-significant decrease in IQ was noted in children receiving phenobarbital at 6 and 12 months after treatment onset. Auditory event-related potentials were altered in children receiving phenobarbital. Specifically, an increased P300 latency was found. Because the P300 latency was inversely correlated with IQ, the authors suggest that P300 latency is a sensitive measure of anticonvulsant effects that reflects subtle cognitive dysfunction. Due to the well-controlled design of this study, this appears to be an appropriate interpretation of the results.

Upon first examination of the research conducted thus far on the cognitive effects of phenobarbital in young children, it is difficult to ascertain what accounts for the disparate results and conclusions of the various studies. The

groups of children employed in the various studies appear to be similar in terms of age, seizure type, seizure severity, and seizure frequency, and phenobarbital dosage taken. However, upon close examination of the studies, there appears to be evidence that phenobarbital has little effect on cognitive functions unless it is taken over an extended period (i.e., ≥ 2 years). All well-designed studies that employed random assignment to conditions and placebo control found minimal to no evidence of intellectual deterioration within the first year of taking the phenobarbital.¹⁵ The one well-designed study that examined intellectual functioning after an extended period of phenobarbital administration found no acute effects of phenobarbital but did find substantial cognitive effects at 24 and 30 month follow-up testing.¹⁷

Thus, the results of these investigations of phenobarbital monotherapy indicate that chronic administration of this anticonvulsant may have a deleterious effect on IQ that remits within years of treatment cessation. Some evidence of visual-motor and memory dysfunction is also indicated. Because the possible cognitive setbacks of this anticonvulsant are substantial, a serious cautionary note about potential cognitive risks should be given before prescribing phenobarbital. Likewise, individuals receiving this medication should be monitored for clinically important changes in cognition.

Phenytoin

The research investigating the cognitive effects of phenytoin usage is more sparse than that reported with phenobarbital. A summary of studies evaluating the cognitive effects of phenytoin is depicted in Table 2, and comparison trials can be found in Table 3.

Only one study has exclusively focused on the effect that phenytoin has on cognitive functioning in children.²⁴ This study did not compare children exposed to phenytoin with any control group. Instead it compared the performance of 50 children when exposed to various concentrations of phenytoin. However, the within-subject design in which peak and trough phenytoin concentrations were counterbalanced is a methodological strength of this study. Phenytoin concentration was considered high when testing occurred 2.5 hours after medication administration (i.e., peak concentration, mean=4.35

$\pm 3.04 \mu\text{mol/L}$); concentration was considered low when testing preceded medication administration (i.e., trough concentration, mean $= 2.69 \pm 2.44 \mu\text{mol/L}$). Cognitive testing during "peak" versus "trough" phenytoin concentration was conducted on separate days. No consistent change in cognitive function was associated with high or low, peak or trough phenytoin concentration. This study provides limited information about the effect of phenytoin on cognitive functioning because it does not compare phenytoin therapy to a placebo-control condition. The results of this study suggest that greater pheny-

toin concentrations (within the range studied) are not associated with increased cognitive dysfunction. No conclusions can be drawn about the cognitive effects of phenytoin outside of the range of concentrations studied.

The effects of phenytoin on memory performance compared to carbamazepine are controversial. One study compared the relative influence of phenytoin and carbamazepine on memory, reaction time, and perceptual-motor coordination in children newly diagnosed with tonic-clonic and partial seizures.²⁵ No mention of random assignment was made. Therefore, it

Table 3

Reference (N)	Population	Study Design	Measure Used*	Findings
PHENOBARBITOL vs CARBAMAZEPINE				
20 (18 PB, 15 CBZ)	2-12 yrs; Newly-diagnosed partial onset sz; IQ >60 No difference in age or gender	B, WS, DB, R, initiation study. Testing at baseline, 6, and 12 mo	Children < 6 yrs; McCarthy Scale of Children's Abilities <i>Children ≥ 6 yrs</i> ; WISC-R and Raven's Prog. Matrices	no significant change in IQ for either group; no difference between groups on Raven's Progressive Matrices (used as nonverbal intelligence scale)
PHENOBARBITOL vs VALPROIC ACID				
21 (32 PB, 32 VPA 60 controls w/o epilepsy)	4-12 yrs No description of sz.; All attended ordinary school, no mental retardation or neurologic abnormalities; treatment >6 mo at first testing; No matching described	B, WS, not R. Testing at beginning of study, repeated after 9-12 mo	WISC	at first testing the PB group significantly lower FSIQ (9 points) & PIQ (10 pts) than controls;† VPA group was not significantly different than controls; significant improvement in scores from first to second testing for controls (FSIQ=6 pts; VIQ=3 points; PIQ=5 pts) and VPA group (FSIQ=6 pts; PIQ=7 pts);† PB group showed no improvement
22 21 (exposed to both PB and VPA)	6-14 yrs with old Normal IQ; partial or tonic-clonic sz; no difference in sz control	R, B, PC cross-over for 6 mo., counterbalanced	WISC-R, Detroit Tests of Learning Apt, Sym Digit, Bender-Gestalt, Berkeley Paired Assoc, Seashore Rhythm, WRAT, Gray Oral, Ambulation Backward, Mazes, Finger Tapping, Video Arcade Games, Cont. Performance Test	Children performed significantly worse while receiving PB than VPA on: Block Design (1 pt);† PIQ (5.3 pts);† FSIQ (3.8 pts);† Berkeley Paired Associate Learning I (2 pts) and II (3 points);† no other significant differences
PHENOBARBITOL vs CARBAMAZEPINE vs VALPROIC ACID				
23 (25 PB, 26 CBZ, 25 VPA)	7-15 yrs; variety of sz types; History ≥2 sz; No prior AED exposure; no matching described	B, WS, R; Testers were blind to AED initiation study; Testing at baseline, 6 and 12 mo after treatment onset	WISC-R, Bender-Gestalt test, Evoked-Potential: P300 amplitude and latency	no differences in IQ between groups at any testing time or change in IQ over time for any AED; although PB group did show non-significant decrease over time; Increased P300 latency found in PB group at 6 and 12 mo significant correlation between P300 and FSIQ in PB group
CARBAMAZEPINE vs VALPROIC ACID				
33 (29 CBZ, 34 VPA, 47 non-epileptic matched controls)	7-12 yrs; Newly-diagnosed, no prior AED therapy; Attending mainstream school; Controls matched for same class, gender, age; same teacher judgement of achievement, no "obvious difference in SES"	Not R, B; Full testing battery at baseline and 12 mo post-treatment onset; Partial battery at 1, 3, and 6 mo post-treatment onset	At baseline, 1, 3, 6 and 12 mo: Cancellation; Focal and) sustain. Attention; Story memory; Pegboard; Digit symbol. Only at baseline & 12 mo: abbreviated WISC-R; reading and arithmetic test	At baseline those with epilepsy demonstrated visuomotor difficulties (pegboard and digit symbol); those with partial sz demonstrated lowered performance on cancellation and focal attention; CBZ group demonstrated lower performance than controls on the pegboard at 1 and 3 mo and on sustained attention at 6 and 12 mo;† VPA group demonstrated lower performance than controls on different tasks (focal attention, digit symbol, and cancellation);†
32 (18 CBZ 9 VPA)	4-16 yrs; Newly-diagnosed partial and generalized; no >2 sz; no defined etiology IQ <70, no prior AED treatment; No matching described	Not R, B; Testing at baseline, 6 and 12 mo after AED begun	WISC, Bender-Gestalt, WRAT, Detroit Tests of Learning Aptitude; Combined into composite score	No significant group difference noted at 6 mo; at 12 months, the CBZ group demonstrated significantly lower cognitive composite score than the VPA group (10.58 pts)†
CARBAMAZEPINE vs VALPROIC ACID vs PHENYTOIN				
Reference 26 (23 CBZ, 21 VPA, 20 DPH)	5-14 yrs with newly-diagnosed partial and generalized sz, gender, age, sz type same across groups; sz-free throughout study;	R, testers were blind; Testing at baseline, 1, 6, and 12 mo after treatment onset	Visual recall, Auditory recall, Cancellation Stroop Processing Speed, WISC-R Neale Reading	no difference in sum of memory scores at 1 mo, CBZ group performed significantly more poorly than VPA group at 6 mo, difference increased at 12 mo;† At 1 yr, CBZ demonstrated significantly lower WISC-R FSIQ than DPH group;†

sz=seizures; B=blinded; WS=within subject; R=randomized; PC=placebo controlled; AED=anticonvulsant

*=Measure described in Table 1.

†="Points" reported refer to the difference in standard score performance between medication groups (for between subject design studies) or between test sessions (for within-subject design studies). Test scores used to calculate difference scores were either reported in the original study as standard scores with a mean of 100 and standard deviation of 15, or *t*-scores were converted to standard scores with a mean of 100 and standard deviation of 15 to allow comparison among study findings.

‡=Although these comparisons yielded statistically significant results, clinical significance of the results could not be evaluated because raw scores were reported instead of standard scores.

is assumed that the choice of medication was made by the child's physician. The authors note that children taking phenytoin performed consistently worse than those taking carbamazepine on all measures of memory. However, the only difference that reached statistical significance was on a test of short-term-memory scanning. Children taking phenytoin also demonstrated significantly poorer performance on a measure of perceptual-motor coordination. The authors concluded that phenytoin is associated with a greater number of cognitive side effects than carbamazepine. However, the lack of random assignment of children to medication groups and the lack of strict matching criteria between groups significantly weakens the ability of the authors to draw firm conclusions based on their data.

Forsythe et al. compared the effects of phenytoin versus carbamazepine or valproate on a variety of cognitive functions in 64 children newly diagnosed with epilepsy who were seizure-free over a 12-month period.²⁶ Children with epilepsy were randomly assigned to anticonvulsant treatment and were tested 1, 6, and 12 months after the onset of pharmacologic therapy. Children receiving phenytoin or carbamazepine demonstrated faster speed of processing than children prescribed valproate. Phenytoin did not have an adverse effect on memory scores relative to the scores of children taking carbamazepine or valproate. No significant differences were found among the treatment groups on a test of visual scanning or on the Stroop test. Because of the random assignment to groups, these results appear to be a valid indication of medication effects on the tests administered in this study. Findings of this investigation did not indicate evidence of cognitive impairment due to phenytoin administration. However, because no placebo control was employed, aversive cognitive effects of phenytoin cannot be ruled-out by this study.

Another investigation compared the cognitive effects of discontinuing phenytoin, carbamazepine, and valproate in 58 children with epilepsy.²⁷ A control group that continued pharmacologic therapy was employed, and assignment to groups was not random. Participants were administered tests of psychomotor speed, "mental speed and conceptual processing," short-term memory, and attention. These tests

were given before medication discontinuation, immediately after discontinuation, and 4 weeks after discontinuation. Bilateral psychomotor performance improved for all 3 medication groups upon discontinuation of the drugs and continued to improve at the 4-week post-discontinuation assessment. Attention, mental speed, and short-term memory did not appear to be affected by carbamazepine or valproate. Within-subject comparisons made in this study appear to yield valid results, and phenytoin's deleterious effect on psychomotor performance has been demonstrated in other studies.²⁸

Doddrill found that all significant deficits revealed when giving a full Halstead-Reitan neuropsychological battery of tests could be reduced to nothing by controlling for motor speed.²⁸ Thus, apparent deficits in several different realms of cognitive functioning are likely to reflect slowed psychomotor speed rather than significant neurocognitive deficits. This finding presents a caveat to the spurious interpretation of "higher-order" cognitive processing deficits without statistically controlling for the effects of psychomotor slowing in this population of children.

Carbamazepine

Several studies have investigated the effects of carbamazepine on a variety of cognitive functions. These trials examined the effect of carbamazepine dose and concentration on cognitive functions. A summary of studies evaluating the cognitive effects of carbamazepine are depicted in Table 3 and 4. Seidel et al. examined the effect of carbamazepine on a wide range of cognitive functions in 10 children with benign Rolandic epilepsy.²⁹ Within-subject comparisons were made between performance with and without carbamazepine. Half of the subjects were medicated for the first phase, and they stopped taking the medication prior to the second session; the other 50% were unmedicated during the first phase, and they received carbamazepine prior to the second testing session. Children performed significantly worse on memory for stories when receiving carbamazepine than when they were not taking this medication. No statistically significant differences were found on measures of intelligence, speeded visual search, attention or expressive language. The results of this well-designed study suggest that children

may experience a decline in memory as a result of taking carbamazepine. This result indicates that carbamazepine's effect on memory functioning deserves more attention from researchers.

Aman et al. examined the relationship between fluctuations in carbamazepine concentration and psychomotor performance in 50 children with "well-controlled seizures."³⁰ The effects of both intersubject and intrasubject variation in carbamazepine were assessed. To assess the effect of intersubject carbamazepine concentration differences on behavioral performance, carbamazepine saliva concentration was averaged over two testing days and subjects were divided into "high" (mean=12.24 $\mu\text{mol/L}$) and "low" concentration (mean=18.85 $\mu\text{mol/L}$) groups. Intrasubject variation in carbamazepine concentrations was assessed by varying the time of testing relative to medication administration. Intrasubject carbamazepine saliva concentration was considered to be at a "peak" level (10.34 $\pm$ 2.82 $\mu\text{mol/L}$) when testing occurred 2.5 hours after medication administration; concentration was considered to be at a "trough" level (5.33 $\pm$ 2.32 $\mu\text{mol/L}$) when behavioral testing preceded medication administration. No intersubject differences between high and low saliva concentration groups were found on any cognitive measure. However, when intrasubject cognitive performance was compared at peak and trough concentrations, trough concentration was associated with reduced seat activity and changes in response times (i.e. response time was slowed on some measures and speeded on others). Results of this study are difficult to interpret because they do not present a consistent picture of the effect of carbamazepine concentration on response times. Additionally, comparisons are made within a limited range of carbamazepine concentrations, and no conclusions can be drawn about the effects of carbamazepine concentrations outside of this range. No conclusions can be drawn about the effects of carbamazepine therapy relative to a control group that does not receive carbamazepine.

Numerous comparison studies have juxtaposed the cognitive side effects of carbamazepine with other "older" anticonvulsants. As stated in the section on phenobarbital, when carbamazepine and phenobarbital were directly compared, no difference was found with regard to their impact on intellectual functioning.

To recap findings of comparison studies cited within the review of carbamazepine, the effects of phenytoin on memory performance compared to carbamazepine are controversial. One report has found that carbamazepine has a less deleterious effect than phenytoin on memory, particularly on short-term-memory scanning.²⁵ Other studies found no difference in memory performance between children administered carbamazepine versus phenytoin.^{26,27} Differences in findings may relate to many differences in study designs, including memory measures used and differences in participant characteristics. With respect to comparative effects on other neurocognitive functions, perceptual-motor coordination appears to be less affected by carbamazepine than phenytoin in children with newly diagnosed seizure disorders.²⁵ Carbamazepine treatment is not thought to be associated with greater difficulty with attention, Stroop performance, visual scanning, or speed of information processing than either phenytoin or valproate treatment.^{26,27}

Studies examining the impact of carbamazepine versus valproate on cognitive functioning generally conclude that if there is an impact of either medication, it is minimal. The results of only one study indicated that memory was adversely affected in children prescribed carbamazepine relative to children prescribed valproate.²⁶ All other studies indicate that cognitive functioning is relatively intact in children administered carbamazepine or valproate monotherapy.^{31,32} Stores et al. examined intelligence, focused and sustained attention, memory, visual search ability, and visuomotor coordination in a group of 63 children with newly diagnosed epilepsy.³³ Performance on cognitive measures was assessed at pretreatment and 1, 3, 6, and 12 months after introduction of treatment. A control group of 47 neurologically normal children was included in the study. The authors report that children receiving valproate demonstrated poorer focal attention performance than controls, and children receiving carbamazepine performed worse than controls on measures of sustained attention and visuomotor coordination. Unfortunately, the results of this comparison study are difficult to interpret for 3 reasons. First, assignment of children to the treatment groups was not random, and the authors report differences in characteristics of the children be-

tween the two anticonvulsant groups. Significant findings of anticonvulsant effects on cognition were confounded by effects of seizure because valproate had been prescribed mainly for the treatment of primary generalized seizures, and carbamazepine was typically prescribed for children with partial seizures. Second, some of the decrements in visuomotor and attentional functioning reported to be due to anticonvulsant treatment had also been seen in the testing done prior to the onset of treatment. Third, there is no systematic evaluation of the effects of possible selective attrition of participants at follow-up testing. The results of this study do not present a clear comparison of the relative influences of valproate or carbamazepine treatment on cogni-

tive functioning, although findings of the study suggest that the cognitive side effect profile of both medications is minimal.

Another study evaluated the effect of carbamazepine and valproate on cognitive functioning, intellectual functioning, achievement, and memory in children with partial and generalized seizures at pretreatment and after 6 and 12 months of therapy.³¹ The results show no decline in cognitive performance from pretreatment to posttreatment assessment for either medication. A strength of this study is its use of a within-subject design. However, there was much attrition of participants at each follow-up assessment. Reasons why participants left the study and an analysis of how this attrition af-

Table 4. Carbamazepine and Valproic Acid Studies

Reference (N)	Subject Characteristics	Design	Measures Used*	Findings
CARBAMAZEPINE STUDIES				
29 (10 CBZ)	6-12 yrs ; Benign rolandic epilepsy	WS; 5 subjects tested before treatment; 5 subjects tested after treatment (mean duration 2.1 yrs)	WISC-III; Trials A & B; Continuous Attn Test; Boston Nam; WRAML Tapping; Pegboard	After Bonferroni correction: Performance on WRAML Story Memory during CBZ treatment was significantly worse than performance when not taking CBZ (8 points).† No significant correlation between serum concentration and test performance
30 (50 CBZ)	4-16 yrs; attending normal classes. Most partial & generalized seizures, seizure-free for 2 mo	WS; Testing at high and low salivary CBZ concentrations	Matching Familiar Figures; Aud-Vis Integrat. Test; STM task CPT; seat mvmt; maze task; graduated holes task; pursuit rotor; Porteus maze	CBZ salivary concentration was not significantly related to performance on any measure, High CBZ concentration associated with faster speed on A-V Integration and Matching Familiar Figures Test, slower Speed on STM task, and fewer commission errors on CPT‡. High CBZ concentration associated with reduced seat mvmt during STM‡. Seat movement and CPT errors of commission decreased more markedly in group with partial seizures‡
41 (11 CBZ; 11 healthy controls)	Newly-diagnosed epilepsy matched for age (mean age 9.8 yrs) Complex partial seizures, FSIQ>80; No progressive neurological disease	Initiation study. Testing at baseline, high (3-hr post-dose) and low (12-14 hr pre-administration) CBZ concentrations	CPT; Sternberg paradigm; Paired Assoc; Pegboard; WISC-R; PIAT	Controls demonstrated higher IQ and faster Pegboard performance at baseline comparison, CBZ concentration indirectly correlated with performance on Paired Associates (verbal learning and STM), Sternberg test (STM); directly correlated with Pegboard nonpreferred hand speed (motor speed)
VALPROIC ACID STUDIES				
34 (47 VPA)	4-15 yrs; normal IQ; Most partial & generalized seizures, seizure-free 2 mo	WS; Testing at high and low salivary CBZ concentrations	Matching Familiar Figures; Aud-Vis Integrat; STM task; CPT; seat mvmt; maze task; grad. holes task; pursuit rotor; Porteus maze	Children with low VPA saliva concentration demonstrated better performance on Auditory-Visual Integration† and the Porteus Maze test (16.29 pts)†. Concentration of VPA as measured by latency between medication administration and testing was not related to psychomotor performance

CBZ = carbamazepine; VPA = valproic acid; WS= within-subject

*= test describe in Table 1; † = "Points" reported refer to the difference in standard score performance between medication groups (for between subject design studies) or between test sessions (for within-subject design studies). Test scores used to calculate difference scores were either reported in the original study as standard scores with a mean of 100 and standard deviation of 15, or t-scores were converted to standard scores with a mean of 100 and standard deviation of 15 to allow comparison among study findings; ‡= Although these comparisons yielded statistically significant results, clinical significance of the results could not be evaluated because raw scores were reported instead of standard scores.

affected the study's results were not addressed. It is, therefore, difficult to interpret the results of this study.

Based upon the existing literature, most aspects of neurocognitive functioning do not appear to be affected by carbamazepine. Some reports suggest that memory functioning is mildly compromised by carbamazepine therapy. The tendency for reaction time to be slower during times of "high" versus "low" carbamazepine concentration indicates a possible deleterious effect of carbamazepine on processing speed. However, if carbamazepine does exert an effect on processing speed, it appears to be slight as it is not consistently evidenced in speeded tasks. This reaction time deficit may alternatively reflect a slowing of psychomotor speed.²⁷

Valproate

Research investigating the effects of valproate on cognitive functioning in the pediatric population is restricted to investigations of dose-response effects and comparison studies. A summary of studies evaluating the cognitive effects of valproate is shown in Table 4. Aman et al. conducted an investigation of the relationship between salivary concentration of valproate and psychomotor performance, as well as the relationship between psychomotor performance and the fluctuation in valproate concentration.³⁴ Valproate concentration was assumed to be "high" when testing occurred 2.5 hours after medication administration; concentration was considered "low" when testing preceded medication administration. The authors report that they do not provide quantitative measurements of valproate saliva concentrations because "the validity of sodium valproate measurements is uncertain." Results indicated that when children's salivary valproate concentration was "low," they demonstrated less seat movement during a test of impulsivity than when salivary concentration of valproate was "high." Children with a "low" concentration of valproate also exhibited better performance on a measure that required them to match visual patterns with aural patterns and on a test of maze completion, which is considered a test of practical general intelligence and planning capacity. Concentration of valproate was not related to psychomotor performance. The authors addressed an important caveat in interpreting results of the in-

verse relationship between test performance and valproate dosage by stating that dosage may have been confounded with the severity of the children's epilepsy. As with other studies conducted by Aman et al., results cannot be applied to children receiving medication concentration outside of the range of study.^{24,30}

An investigation by Brouwer et al. used an open-crossover design to compare attention, vigilance, and other neuropsychological performance in 12 children with epilepsy following 4 weeks of conventional valproate (i.e., plain Depakine enteric coated tablets) versus 4 weeks on controlled-release valproate (i.e., immediate release Depakine Chrono tablets).³⁵ No difference in attentional performance was found when children were receiving conventional versus controlled-release valproate. The epileptic children receiving valproate also did not differ from a control group of drug-free, healthy classmates in level of performance on neuropsychological measures. This lack of neurocognitive differences between the epileptic children and controls suggests that seizure disorders were generally mild and provides clear evidence that the valproate had little effect on cognitive functioning in the children with mild seizure disorders. It is not discernable from the results of this study how valproate affects the cognitive functioning of children with more severe epilepsy.

It is important to note that several case studies of children taking valproate report a rare "pseudotumor" of the brain and corresponding dementia. Cognitive and behavioral symptoms associated with "pseudotumor" include decreased motor ability, decreased attention and interest in surroundings, drowsiness, emotional lability, deterioration of speech, intention tremor, difficulty with balance, and ataxia. A decrease in full-scale IQ has also been noted.³⁷ These reports indicate that dementia may develop shortly after the introduction of the valproate,^{36,37} or the dementia may have an insidious and progressive course that becomes obvious only after chronic treatment.³⁸ Both the encephalopathy observed on MRI scans and the cognitive changes remit within days of discontinuation of the medication.

In review of findings about the cognitive effects of valproate cited and described in prior sections, with the exception of *rare* cases in which chronic valproate administration has led to re-

versible encephalopathy and dementia, valproate does not appear to have a negative effect on most neurocognitive functions. Although data suggesting that speed of information processing may be slower in children randomly assigned to take valproate,²⁶ intellectual functioning, achievement, or memory in children after 6 and 12 months of treatment appear to be unaffected.³² This difference in speed of information processing was seen at the 1 month assessment but not at 6 or 12 months, and, therefore, appears to be only a transient effect of valproate on cognitive functioning. There is also evidence that valproate administration may result in bilateral psychomotor slowing.

METHODOLOGICAL CRITICISMS

The literature concerning pediatric neurocognitive effects of phenobarbital, carbamazepine, valproate, and phenytoin is riddled with methodological difficulties. Some of these difficulties are due simply to poor study designs, and some methodical obstacles are difficult or impossible to overcome in human studies due to ethical considerations relating to the safety and health of the young study participants. This section will outline these various difficulties and delineate the limitations they pose to interpretation of study findings. Conclusions that can be drawn from the existing literature will be outlined, and future directions for research will be suggested.

Lack of equivalency in groups compared

In an ideal study, groups that are compared are equivalent in all respects except for one variable that is manipulated experimentally. In a study with these characteristics, one could draw the unequivocal conclusion that any difference in outcome found between the groups was due to this experimental manipulation. Two primary methods of creating equivalency between or among groups are through use of a within-subject design or through a between-subject design that employs random assignment of individuals to different conditions. Several studies employed one of these two designs.^{15-17,19-24,26,29,30,34} However, some between-subject studies did not use random assignment, instead examining cognitive effects of anticonvulsants that had previously been prescribed by physicians. This lack of ran-

dom assignment is often necessary due to ethical considerations, but investigators that cannot employ random assignment must employ other techniques to control for variability between groups on factors that are not the subject of study.

The two main methods used to do this are: matching of participants on critical characteristics to attain equivalency between groups or utilizing statistical methods of covariance to control for variability in characteristics that are not the focus of the present research endeavor. As discussed in the first section of this paper, there are numerous characteristics of children with epilepsy other than medication choice (e.g. seizure type, frequency, etc.) that have potential effects on cognition. Therefore, if groups compared in a study of medication effects differ on any of these other characteristics and this variability is not controlled statistically, it is difficult to determine whether difference in cognitive ability between groups is due either to medication effects or effects secondary to other characteristics that are not equivalent between groups. Within the body of literature reviewed in this paper, several of the between-subject comparisons of medication effects on cognition were done without proper experimental or statistical control of variables of non-interest. Therefore, conclusions about medication effects should not be deduced from these comparisons.^{32,33} Improperly controlled between-subject comparisons were even found in studies that also included well-designed within-subject comparisons.^{20,21,23} Again, conclusions drawn from these between-subject comparisons are spurious.

Selection Bias

There is an overwhelming preponderance of research being conducted in children that have relatively benign or well-controlled epilepsy. Due to obvious ethical reasons, children with severe and intractable epilepsy cannot be randomly-assigned to medication group, given a placebo in place of medication, or taken off their current medication in order to examine the degree of impairment in cognitive functioning that may be attributed to drug treatment. These methodological tools can only be used to study the cognitive effects of medication on children with mild seizure activity. It is much easier for investigators to construct clean, well-designed studies that examine medication effects in chil-

dren with milder and less frequent seizure activity. Hence, most of what is known about the cognitive effects associated with anticonvulsants comes from studies examining children with mild epileptic activity. These results are not readily generalizable to children with more severe epilepsy.

Unfortunately, it does not appear that it is entirely possible to overcome this paucity of information about the cognitive effects of anticonvulsants in children with severe epilepsy. Most designs that are employed in research simply cannot be utilized in an ethical manner. The only design that can ethically be used to study the cognitive medication effects in severe epilepsy is one in which participants continue to take a medication as prescribed by a physician. As mentioned in the section regarding equivalency between groups, there must be proper matching on critical characteristics such as age of seizure onset, seizure frequency, seizure type, number of medications taken, and serum concentration of medications so that the only significant difference between groups is the medication that they are taking. Through this type of careful design, we can arrive at clear conclusions, and we can gain knowledge about the relative effects of different medications on cognitive processing in children with severe forms of epilepsy.

Attrition

Methodological criticisms about attrition pertain only to those studies that contain a follow-up or longitudinal component. In all longitudinal studies included in this review, only one reported that no subjects left the study from initial assessment to follow-up. Although other longitudinal studies reported attrition in their participant groups with each successive follow-up, it was rare that authors described how this attrition affected the make-up of the groups. Reporting the characteristics of participants that leave a study is important because it is possible that departing participants share important characteristics. Attrition has a greater negative effect on the integrity of between-subject designs because it can undermine the assumption that comparison groups are equivalent in all respects other than treatment administered. For example, within a longitudinal study employing random assignment of children to medication or placebo, it is likely that several children within the pla-

cebo group will leave the study before follow-up evaluation due to a worsening of seizure activity. Also, children that leave the placebo group are likely to have a greater frequency of seizure activity than children that do not leave the placebo group. Therefore, at follow-up it is possible that the group randomly assigned to medication has a higher average seizure frequency than the placebo group because of selective attrition from the placebo group. Results that indicate that cognitive ability is more negatively affected in the medication group could be due to either medication effects on cognition or lowered cognitive ability due to greater seizure frequency. Clearly, medication effects are confounded by the effects of seizure severity; hence, no clear conclusions can be drawn about the effect of medication on pediatric cognition.

The integrity of within-subject designs is less affected by attrition because participants serve as their own controls. However, it is still probable that the conclusions from within-subject studies are also affected by selective attrition of participants. It is likely that participants who terminate participation in medication studies have greater seizure severity or frequency. Therefore, it is unlikely that the results of the many medication studies will generalize well to children with more severe seizure activity.

The methodological flaw of ignoring the effects of attrition on follow-up results is pervasive in this body of literature and limits the conclusions that can be made about the chronic effects of these medications on pediatric cognitive skills. Reporting standards must be raised and statistical comparisons of characteristics of subjects should be in regular practice to insure that the follow-up components of studies are as methodologically sound as the initial comparisons.

CONCLUSIONS

This review of four "older" anticonvulsant medications (phenobarbital, carbamazepine, valproate, and phenytoin) indicates that there are few cognitive side-effects of these medications in children. Chronic administration of phenobarbital is the only treatment that appears to have a clear, clinically-significant impact on the cognitive ability of pediatric patients. All other medications are relatively innocuous in this respect. The cognitive effects that have been reported for

carbamazepine, valproate, and phenytoin have not been replicated consistently in all studies. The majority of conclusions are limited to those children with relatively mild seizures and limited seizure frequency. Unfortunately, little research has focused on cognitive side effects of anticonvulsants in children with severe and intractable epilepsy. Therefore, future research should target children with more severe epilepsy. Although this research is difficult to perform, there is a need for more information regarding how severe seizure activity and anticonvulsants interact to affect pediatric cognition. Additionally, closer attention must be paid to proper experimental and statistical control to insure that clear conclusions about medication-associated cognitive impairment can be reached from the

DRUG	Reference Range	
	CONVENTIONAL UNITS	SI UNITS
Carbamazepine	4–12 µg/mL	17–51 µmol/L
Phenytoin	10–20 µg/mL	40–80 µmol/L

research done.

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