



Neuro UpdateSM

PERFORMANCE OF CHILDREN TREATED FOR SEIZURES WITH MONOTHERAPY MEDICATION BY MEASURING INTELLECTUAL FUNCTIONING

Kristine B. Whigham, Psy.D.

Thomas G. Burns, Psy.D., A.B.P.P.-C.N.

Epilepsy is a chronic disorder affecting more than 4 percent of children.¹ Given the involvement of the central nervous system and potential cognitive difficulties and/or changes in cognitive and behavioral functions over time, the role of the neuropsychologist is especially relevant.² Neuropsychological evaluations provide information regarding a child's current cognitive, behavioral and emotional functioning in the context of a seizure disorder and associated neuropathology. Additionally, evaluations identify appropriate interventions and accommodations for the classroom and home environments. Neuropsychological evaluations often are performed to obtain a baseline of neurocognitive functioning prior to, or at the outset of, an intervention and to track changes over time with respect to multiple factors (changes in seizure variables, medications and school demands).

For many children, underlying brain pathology is the most significant cause of cognitive impairment; however, other factors—including seizure variables (age of onset, seizure type and seizure frequency), psychosocial issues and antiepileptic drug (AED) therapy—also may impact cognition. The adverse effect of an AED is one factor that potentially can be alleviated. Due to the growing number

of available AEDs, the goal of obtaining greater control over seizures with fewer or no cognitive side effects has become an increasingly important area of study. Research investigating the cognitive effects of specific AEDs has been inconsistent, often due to methodological problems, such as differences in study designs, small sample size and variability in side effect reporting and analysis.

Continued on Page 2

However, polytherapy has been associated with greater adverse cognitive effects than monotherapy, and although there is comparatively little research about newer AEDs, they are considered to have more favorable cognitive profiles than older AEDs, with the exception of topiramate.³ Most research has focused on adults. There have been a few reviews about how AEDs affect cognitive functions in pediatric populations.^{4,5}

However, more studies are needed, particularly for newer AEDs. In general, AEDs have been implicated in contributing to memory impairment, word-finding problems, mental slowing, attention deficits, impulsivity, hyperactivity, irritability, sedation, insomnia, aggression, depression and suicidal ideation.

As medication options increase, the consideration of cognitive side effects is becoming more important in deciding which medication may be most appropriate for a particular child. From a neuropsychological perspective, understanding how AEDs affect an individual's cognitive functioning using specific measures is important when interpreting neuropsychological test results. It is particularly important when comparing changes in cognitive test scores over time (e.g., Is a decline in test scores related to changes in medication, and therefore differences in medication side effects, or do test scores indicate a true regression in skill?).

The following is a preliminary analysis that was conducted in an effort to examine the possible effects of monotherapy on a child's performance using the Wechsler Intelligence Scale for Children—Fourth Edition.⁶ The WISC-IV is a commonly used measure of overall cognitive ability. The core WISC-IV battery consists of 10 subtests that comprise four indices:

- Verbal Comprehension Index
- Perceptual Reasoning Index
- Working Memory Index (WMI)
- Processing Speed Index (PSI)

This analysis included four AEDs: divalproex sodium, levetiracetam, lamotrigine and oxcarbazepine. Based on a review of the literature, the following hypotheses were considered:

- H1. Children undergoing monotherapy treatment with levetiracetam, lamotrigine and oxcarbazepine (newer AEDs) will perform similarly on WISC-IV indices and core subtests to matched controls, while children taking divalproex sodium (an older AED) will perform significantly lower on WISC-IV indices and core subtests when compared to matched controls.
- H2. Children taking divalproex sodium will perform significantly lower on WISC-IV indices and core subtests when compared to children taking levetiracetam, lamotrigine and oxcarbazepine.

METHODS

Participants

Participants in the clinical group were selected from a larger group of children referred for neuropsychological evaluation at Children's Healthcare of Atlanta. An archival search was performed to identify children who were on monotherapy for the treatment of seizures and who were administered the WISC-IV. Medications were limited to divalproex sodium, levetiracetam, lamotrigine and oxcarbazepine, as these are the most commonly prescribed medications among children seen within this department. Children with comorbid neurological conditions, with the exception of attention-deficit/hyperactivity disorder (ADHD), were excluded. The search yielded 80 children.

Clinical participants were matched to controls by age, gender, ethnicity (when possible) and geographical region (all participants were from the southeast). The control group consisted of 80 children obtained, with permission from the publisher, The Psychological Corporation, from the standardization sample of the WISC-IV. Statistical analyses revealed no significant differences between the clinical and control groups for age, gender, ethnicity or geographical region.

RESULTS

- H1a. An independent samples t-test indicated that children treated for seizures with monotherapy ($n = 80$) performed significantly worse on all WISC-IV factor index scores, as well as most core subtests, compared to controls ($n = 80$).
- H1b. When specific medications were examined, findings indicated that all four medications were associated with significantly poorer performance on the PSI, and three out of four medications (divalproex sodium, levetiracetam and oxcarbazepine) were associated with lower scores on the WMI when compared to controls.
- H2. A one-way ANOVA indicated that WMI scores for children taking divalproex sodium were significantly worse than scores for those taking oxcarbazepine.

DISCUSSION

These findings indicate that children taking monotherapy AED treatment (regardless of medication type) obtain lower scores on certain WISC-IV indices, particularly the WMI and PSI, when compared to controls. In addition, children taking divalproex sodium obtain significantly lower WMI scores than children taking oxcarbazepine. This latter finding is consistent with research demonstrating that older AEDs tend to be associated with greater cognitive side effects than newer AEDs. While WMI and PSI scores were generally within the low average to average range for children taking levetiracetam, lamotrigine and oxcarbazepine, they were within the borderline range for children taking divalproex sodium.

It is important to note that multiple factors—including underlying brain pathology, psychosocial issues and seizure variables (age of onset, seizure type, seizure frequency)—may impact cognition.

However, given the increasing number of available medications, a greater understanding of the side effect profile for specific medications will help clinicians minimize the possible side effects caused by medications that negatively impact learning. While there is a definite need for prospective, well-controlled studies examining the effects of AEDs on children's performance across measures of intellectual ability and other cognitive tests, the above analyses investigating four commonly prescribed AEDs on WISC-IV performance lend support for the need to evaluate cognitive skills prior to initiating, adding to or changing an AED regimen. Changes sometimes can be subtle and require thorough evaluation. This would allow clinicians to monitor and track cognitive side effects and determine whether adjustments in medication or academic accommodations are needed.

References

1. Wilfong, A. A. (2007). Monotherapy in children and infants. *Neurology*, 69, S17-S22.
2. Nelson, E., & Fischer, M. (2007). Neuropsychological evaluation of the child with epilepsy. *Disease-a-Month*, 53, 162-168.
3. Aldenkamp, A. P., De Krom, M., & Reijs, R. (2003). Newer antiepileptic drugs and cognitive issues. *Epilepsia*, 44, S21-S29.
4. Bourgeois, B.F.D. (2004). Determining the effects of antiepileptic drugs on cognitive function in pediatric patients with epilepsy. *Journal of Child Neurology*, 19, S15-S24.
5. Loring, D.W., & Meador, K.J. (2004). Cognitive side effects of antiepileptic drugs in children. *Neurology*, 62, 872-877.
6. Wechsler, D. (2003). *WISC-IV Technical and Interpretive Manual*. San Antonio, TX: The Psychological Corporation.



Children's Healthcare of Atlanta
1699 Tullie Circle NE
Atlanta, GA 30329-2321

First Class Presort
U.S. Postage
PAID
Permit No. 0525
Atlanta, GA

Neuro Update

Published quarterly by Children's Healthcare of Atlanta, 1699 Tullie Circle NE, Atlanta, GA 30329-2321

NEURO UPDATE BY E-MAIL

Would you like to receive *Neuro Update* via e-mail? If so, send an e-mail, with Sign Up in the subject line, to NeuroUpdate@choa.org. You will receive an online version of *Neuro Update* each quarter.

QUESTIONS/COMMENTS

Call Neuropsychology Services at Children's at 404-785-2849, or visit our Web site www.choa.org/NeuroUpdate for more information.

Earn CME Credit Online

Children's Healthcare of Atlanta now offers one hour of continuing medical education (CME) credit online at www.choa.org/neuroupdate. To earn the credit, read three issues of *Neuro Update* and complete the questionnaire at the end of each issue. When you have completed each component within Module I and Module II, you will earn one hour of CME credit for each module.

Children's Healthcare of Atlanta is accredited by the Medical Association of Georgia to provide continuing medical education for physicians. Children's designates this educational activity for a maximum of 1 AMA PRA Category 1 Credits™. Physicians should only claim credit commensurate with the extent of their participation in the activity.