# Cognitive and Behavioral Side-Effects among Seizure Controlled Epileptic Children: The Impact of Treatment for Monotherapy with Antiepileptic Medication

Tajiri, Tiffany, Burns, Thomas G., Luton, Lindsay M., & Whigham, Kristine B.

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## INTRODUCTION

Cognitive and behavioral dysfunction related to antiepileptic drug (AED) therapy in children is a critical concern given the potential negative side effects of treatment on school performance and learning. Unfortunately, physicians often have incomplete data on which to base treatment decisions since randomized controlled trials of newer AEDs have not included childhood epilepsy (Wilfong, 2007). The selection of an appropriate AED for initiation of monotherapy requires careful assessment of its' potential risks and benefits.

Research suggests that monotherapy is associated with fewer potential problems than polytherapy. The surfacing of monotherapy as a mainstay treatment resulted from studies that demonstrated the advantages and effectiveness of a single AED in controlling seizures (Sachdeo, 2007).The most recent generation of AEDs generally have more favorable cognitive and behavioral profiles than older treatment options (Aldenkamp, De Krom, & Reijs, 2003). As the medication options increase, consideration of cognitive and behavioral side effects becomes a more prevalent issue. Unlike adults, the cognitive and behavioral side effects of AEDs in children occur during critical periods of development, hence treatment decisions made in childhood may have life long implications (Loring, 2005). Nonetheless, most of the research on AED therapy has been performed on adults, while there has been a dearth of research on the effects of AEDs on cognitive and behavioral functioning in pediatric populations (Bourgeois, 2004). The objective of this study was to evaluate and compare the cognitive, executive, and behavioral functioning among children with epilepsy and neurotypical controls.

## 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 (n = 93). An archival search was performed to identify children who were on monotherapy for the treatment of seizures and had been evaluated using the *Wechsler Intelligence Scale for Children-Fourth Edition (*WISC-IV), the *Behavior Assessment System for Children-Second Edition* (*BASC-2*) and the *Behavior Rating Inventory of Executive Function* (*BRIEF*). Medications were limited to divalproex sodium, levetiracetam, lamotrigine, and oxcarbazepine since these are the most commonly prescribed medications used to treat children with this condition. Children with co-morbid neurological conditions were excluded, with the exception of ADHD, which is commonly diagnosed in children with epilepsy.

Participants in the control group were neurotypical children who were recruited by the Friends Research Fund of Children's Healthcare of Atlanta to participate in an unrelated neuropsychological study (n = 42). Similar to the epilepsy cohort, these children were also assessed using the *WISC-IV, BASC-2,* and *BRIEF.*

| Variable | Clinical Group | Control Group |
|---|---|---|
| ***Gender (n, %)*** | | |
| Female | 41 (44%) | 18 (43%) |
| Male | 52 (56%) | 24 (57%) |
| ***Age*** | | |
| Mean | 11.67 | 12.61 |
| SD | 13.82 | 3.80 |

**Medications (Clinical Group Only)**

| | |
|---|---|
| Divalproex sodium | n=13 |
| Levetiracetam | n=19 |
| Lamotrigine | n=21 |
| Oxcarbazepine | n=27 |

### Statistical Analysis

Using SPSS version 12.0 statistics package, a MANOVA and post hoc analyses were conducted to compare the *WISC-IV* FSIQ scores and the *BASC-2* and *BRIEF* index scores between the clinical and control groups. The clinical group was further broken down into four subgroups based on the monotherapy treatment utilized (i.e., levetiracetam, lamotrigine, oxcarbazepine, or divalproex sodium).

## RESULTS

Results from a MANOVA with post-hoc analyses indicated that each of the epilepsy cohorts performed worse than normal controls on intelligence testing, regardless of which antiepileptic medication was prescribed ($p \leq .001$ for all AED groups). Similar findings also emerged on the *BRIEF* composites, suggesting that all AEDs have an adverse effect on executive function when compared to normal controls ($p \leq .01$ for all AED groups). In contrast, medication-specific differences were apparent on indices of the *BASC-2*, as the levetiracetam cohort was comparable to normal controls on the Internalizing (p=.09) and Externalizing (p=1.0) composites, while the oxcarbazepine group was comparable to the control group on the Externalizing index, alone (p=1.0). Further, while all epilepsy participants were worse than controls on the Adaptive Skills and Behavior Problems indices, a significant difference emerged between the oxcarbazepine and divalproex sodium cohorts on the latter composite, with the divalproex sodium group rated as having more difficulties in this domain (p<.001).

| | Divalroex Sodium | | Levetiracetam | | Lamotrigine | | Oxcarbazepine | | Controls | |
|---|---|---|---|---|---|---|---|---|---|---|
| **WISC-IV** | Mean | SD | Mean | SD | Mean | SD | Mean | SD | Mean | SD |
| Full Scale IQ | 81.00 | 21.12 | 89.79 | 19.98 | 82.90 | 16.49 | 91.00 | 14.86 | 108.13 | 14.98 |
| **BASC-2** | Mean | SD | Mean | SD | Mean | SD | Mean | SD | Mean | SD |
| Internalizing Problems | 114.62 | 17.69 | 104.53 | 17.32 | 112.05 | 20.25 | 106.88 | 15.45 | 92.95 | 10.72 |
| Externalizing Problems | 112.69 | 28.29 | 101.10 | 14.78 | 110.90 | 14.29 | 99.22 | 13.85 | 95.68 | 9.43 |
| Behavioral Symptoms Index | 125.54 | 22.75 | 110.89 | 17.05 | 117.29 | 15.08 | 108.00 | 13.86 | 93.98 | 9.36 |
| Adaptive Skills | 80.31 | 13.94 | 90.21 | 14.63 | 87.61 | 15.74 | 90.15 | 12.18 | 110.50 | 12.26 |
| **BRIEF** | Mean | SD | Mean | SD | Mean | SD | Mean | SD | Mean | SD |
| Behavioral Regulation Index | 124.30 | 22.65 | 107.05 | 18.46 | 113.57 | 19.34 | 106.56 | 15.85 | 88.47 | 28.04 |
| Metacognition Index | 128.31 | 19.61 | 124.32 | 20.70 | 118.57 | 17.70 | 120.22 | 14.09 | 90.03 | 28.89 |
| General Executive Composite | 129.08 | 21.40 | 119.05 | 20.15 | 117.86 | 19.62 | 116.85 | 13.60 | 89.45 | 28.26 |

*Significant findings:*
**p≤.001*
**p≤.01*

## DISCUSSION

These findings indicate that children on monotherapy AED treatment generally perform less well than neurotypical children on measures that assess cognitive, behavioral, and executive functioning. However, on the indices of the *BASC-2*, the clinical group on Levetiracetam performed comparable to normal controls on the Internalizing and Externalizing composites, while the oxcarbazepine group was comparable on the Externalizing index, alone. Further, while all epilepsy participants were worse than controls on the Adaptive Skills and Behavior Problems indices of the BASC-2, a significant difference emerged between the oxcarbazepine and divalproex sodium cohorts on the latter composite, with the divalproex sodium group being rated as having more difficulties in this domain. This later finding is consistent with research demonstrating that older AEDs tend to be associated with more negative cognitive side effects than newer AEDs.

There are a variety of recommended medications with demonstrated clinical efficacy from which to choose depending on the type of seizure, the specific epilepsy syndrome, seizure frequency, and age of onset. Unfortunately, the paucity of research on the cognitive and behavioral side effects in children on AED's has made it considerably more difficult to select the most appropriate medication. When treated with AEDs that are associated with better neuropsychological outcomes, it is possible for children to improve their school performance while reducing their need for special services. Future research should explore prospective long term studies of AEDs with an eye toward cognitive and behavioral side effects in different applications to determine which drugs and which factors may affect school performance, learning, and psychosocial functioning during the school years.

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