Current Literature

In Clinical Science

First-Degree Relative Risk: In Utero Levetiracetam and Valproate Exposure

In Utero Exposure to Levetiracetam vs Valproate: Development and Language at 3 Years of Age.

Shallcross R, Bromley RL, Cheyne CP, Garcia-Finana M, Irwin B, Morrow J, Baker GA; for the Liverpool and Manchester Neurodevelopment Group; UK Epilepsy and Pregnancy Register. In utero exposure to levetiracetam vs valproate: development and language at 3 years of age. *Neurology* 2014;82:213–221.

OBJECTIVE: To compare the cognitive and language development of children born to women with epilepsy (WWE) exposed in utero to levetiracetam (LEV) or sodium valproate (VPA) and control children born to women without epilepsy not taking medication during pregnancy. **METHODS:** The children, aged between 36 and 54 months, were recruited from the United Kingdom and assessed using the Griffiths Mental Development Scales and the Reynell Language Development Scale. Maternal demographic and epilepsy information was also collected for use in statistical regression. This is an observational study with researchers not involved in the clinical management of the mothers enrolled. **RESULTS:** After controlling for confounding variables, children exposed to LEV in utero ($n = 53$) did not differ from unexposed control children ($n = 131$) on any scale administered. Children exposed to VPA ($n = 44$) in utero scored, on average, 15.8 points below children exposed to LEV on measures of gross motor skills (95% confidence interval [CI] -24.5 to -7.1, $p < 0.001$), 6.4 points below on comprehension language abilities (95% CI -11.0 to -1.8, $p = 0.005$), and 9.5 points below on expressive language abilities (95% CI -14.7 to -4.4, $p < 0.001$). **CONCLUSION:** The current study indicates that children exposed to LEV in utero were superior in their language and motor development in comparison to children exposed to VPA. This information should be used collaboratively between health care professionals and WWE when deciding on women's preferred choice of antiepileptic drug.

Commentary

The burdens of epilepsy can be many, ranging from general health risks from poorly controlled seizures, expense of treating a chronic medical condition, to cognitive and behavioral comorbidities associated with the underlying biologic substrate and epilepsy management. Although there are many ways that living with epilepsy can affect family members, there is likely no greater concern to women taking AEDs than the potential effects of taking AEDs during pregnancy on their unborn children. Differential AED effects on developmental outcomes are not only relevant when choosing an AED when multiple treatment options with equivalent efficacy are available, but also in patients where only a single AED has been demonstrated to optimally manage seizures.

A methodological limitation of studies investigating differential risks of in utero AED exposure is their purely observational nature because treatment randomization is impractical and also raises ethical concerns. When multiple independent studies observe the same pattern of drug risk,

however, confidence increases that the pattern represents a true signal rather than reflecting chance differences from nonreplicated trials. Through a series of studies from different institutions, the greatest risk of in utero AED exposure across commonly prescribed AEDs is with valproate (VPA) for both poor anatomic and behavioral outcomes (1–6). Another limitation in establishing AED exposure risks is the large number of AEDs used to treat epilepsy; obtaining adequate sample sizes for each AED can be difficult in addition to study execution pragmatics associated with a complex design including expense. Thus, our knowledge of treatment risks is limited to a few commonly used AEDs, and relative treatment risks have not been formally established for AEDs that have been investigated.

To further establish differential in utero AED treatment risks, Shallcross et al. examined developmental outcome following levetiracetam (LEV) or VPA exposure. The same group of investigators had previously examined outcomes for LEV at <24 months (7), but the present study examines outcomes at an older age, which offers a better measure of long-term outcomes. A particularly valuable component of their study design was the inclusion of a nonexposed control subject cohort of similarly aged children, which for reasons largely attributable to costs of study execution, had been absent in most

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prior studies. The authors observed that children exposed in utero to VPA performed more poorly across a battery of developmental motor and cognitive tasks compared with both LEV and controls. In addition, LEV exposure was not associated with developmental differences compared to control children, which is important given the increasing use of LEV during pregnancy. These results indicate that for women of child-bearing potential, in which comparable treatment efficacy can be anticipated, LEV should be one of the preferred treatment options over VPA whenever possible.

What was not directly quantified, however, were the relative risks of diminished development outcome for exposure to either AED, with results discussed based upon levels of statistical significance. Probability levels derived from VPA and LEV exposed children, which differed by a factor of 2 in size (LEV = 65; VPA = 132), formed the basis of their analyses rather than also presenting effect sizes which would be sample size independent. In addition, group comparisons were made using outcomes that were statistically adjusted for confounding differences between the groups, although results of unadjusted performances are also reported and discussed. Thus, readers characterizing signal strength based solely on levels of statistical significance may easily be misled. More importantly, however, although the report nicely demonstrates differential exposure risk between LEV and VPA, that risk is not quantified. When adverse behavioral outcomes are dichotomized and characterized as “harms” (8), contemporary evidence-based medicine tools such as relative risk or number needed to harm are easily calculated, which are more easily incorporated to guide good clinical practice.

A limitation associated with neuropsychological outcomes of treatment intervention is that the clinical meaningfulness of various neuropsychological scores has not been clearly established for most measures. One of the most common approaches in epidemiology is to characterize samples based upon the frequency of Full Scale Intelligence Quotient (IQ) scores that are less than 70. This approach, however, is likely inappropriate for healthy children who appear to have scores in the normal ranges. Options for future studies to consider is inclusion of outcome characterization based upon a higher IQ threshold, or using difference scores between maternal IQ and child’s overall developmental level at an established threshold (e.g., 1/2 SD) as an indirect approach to characterize suboptimal cognitive outcomes that could be attributed to treatment intervention. Dichotomous outcomes more easily permits relative risks between AEDs to be quantified and communicated to patients.

Another factor for characterizing treatment risks across studies is the specific measure used to establish behavioral outcome. Because a single trial examining all monotherapy AEDs will never be performed, it is important for the clinical research community to agree upon common research standards to facilitate data aggregation whenever possible. This is the goal of the NIH Common Data Elements (CDEs) initiative (9), but in addition to facilitating comparison or data aggregation across studies, characterizing cognitive outcomes using the same measures also permits relative risk calculations across medications based upon the same outcome metric. This is not a criticism of the Shallcross study, which was initiated prior to development of CDEs, but serves to highlight the benefits that

can be derived when studies performed at different institutions employ CDEs for both sample characterization as well as clinical outcome.

Why is relative risk such a valuable statistic, particularly given the consistency of evidence of VPA’s association with poorer developmental outcome? In many cases, precise risk estimates are less important because equally effective AEDs are often available without the same in utero exposure risk as VPA. As implied by Shallcross et al. when discussing the distribution of epilepsy types in their report, however, patients with generalized epilepsy are more likely to be treated with VPA compared with patients with focal epilepsy. Unfortunately, there are some women in whom their best treatment efficacy is achieved only with VPA. Thus, unlike focal epilepsy, in which multiple treatment options are available making it easier to avoid VPA exposure, women with generalized epilepsy may present with a more difficult treatment dilemma. Operationalizing the relative AED exposure risks will provide important information for physicians and patients to weigh against the risk of increased seizures associated with changing AED therapy.

Shallcross et al. not only provide additional information confirming the risk of VPA exposure in a new cohort of children, but also demonstrate developmental outcomes associated with LEV do not differ significantly from nonexposed controls, at least at age 3 on specific outcome measures. It will be important to reproduce this finding in another cohort and to have longer term follow-up using measures of developmental outcomes, and particularly to incorporate constructs that have not yet emerged such as sustained attention, freedom from distractibility, and ultimately school achievement, to confidently conclude that LEV poses no development risk when taken during pregnancy.

by David W. Loring, PhD

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