# WriteClick: Editor's Choice

**Editors' Note:** Drs. Maheshwari et al. and the article by Hernandez-Diaz et al. discuss questions of methodology in regards to the study "Comparative safety of antiepileptic drugs during pregnancy." In reference to the article by Hu et al., "Plasma multianalyte profiling in mild cognitive impairment and Alzheimer disease," in which several peripheral proteins associated with AD are proposed, Dr. Bennett cautions against false-positives and other confounding factors inherent in genome studies.

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## COMPARATIVE SAFETY OF ANTIEPILEPTIC DRUGS DURING PREGNANCY

**Amit Maheshwari, Sunil Athale, O.P. Lekhra, Kapil Telang, Indore, India:** Due to the increased use of newer antiepileptic drugs (AEDs), we agree with Hernandez-Diaz et al. that it is vital to assess the efficacy and safety of the same drugs in the general population and in pregnant women, especially regarding teratogenicity.[1] We also agree that valproic acid use is not acceptable during pregnancy.

The authors excluded spontaneous abortion cases, which reveals a bias because even "safer" drugs like lamotrigine may play a role in these cases. Fetotoxicity of the less "teratogenic" drugs was not considered because only stillbirths and live births were included.[1] Lamotrigine levels drop by more than 50% in pregnancy.[2] The actual serum levels of lamotrigine are unclear in this study. If the doses had been escalated to target nonpregnant levels, there may have been more teratogenic effects.

Finally, the most efficacious drug—valproic acid—was the most teratogenic. Valproic acid has prevented maternal seizures in a significant number of cases and more than any other newer drugs mentioned in this study. Uncontrolled seizures are embryopathic. Stillbirths, microcephaly, mental retardation, and nonfebrile seizure disorders occurred more frequently in the offspring of women with seizure disorders.[3]

This finding in itself may negate the teratogenic effect directly attributable to valproic acid. Valproic acid should not just be viewed in terms of its teratogenicity because up to a low therapeutic dose it is still safe (figure 1[1]).

**Author Response: Sonia Hernandez-Diaz, Lewis B. Holmes, Boston:** We excluded spontaneous abortions because there was not enough information as to whether the embryo had—or was going to develop—a malformation. We would have included spontaneous abortions if we had postmortem reports, including the results of chromosome analyses, since 50% of spontaneous abortions are associated with chromosome abnormalities. There is no current information on any of the spontaneous abortions that have occurred among the women enrolled in the North American AED Pregnancy Registry. In general, pregnancy registries are not a good study design to observe the occurrence of spontaneous abortions, as so many occur before the typical gestational age when women enroll. However, spontaneous abortions were excluded from all exposure groups, not only from the lamotrigine group. The proportion of women excluded because of spontaneous abortions, withdrawals, or losses to follow-up did not vary significantly with the specific anticonvulsant. Therefore, it is unlikely for this selection bias to explain the lower risks found for lamotrigine.

We took into account dose changes during the first trimester and did not find a dose effect for lamotrigine.[4–8] Maheshwari et al. question whether serum levels would be a better exposure measurement. We are obtaining these on a subset of women whose doctors' records include levels. We will be analyzing the associations of outcomes, like malformations, in the exposed fetuses in those subsets when the sample size is large enough to be informative.

We did not find a positive association between seizures during pregnancy and a higher risk of malformations. Others found that neither the number of seizures during pregnancy nor having epilepsy increase the risk of having children with major malformations. Therefore, we found it unlikely that epilepsy itself could explain the risks found for valproic acid.

In our population, even low valproate doses were associated with a twofold increased risk of malformations. However, we agree that there are risks associated with seizures during pregnancy and that most pregnant women need to maintain their medication. The challenge is to assess the safest drug for each

individual patient from those that are effective for her type of epilepsy.




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## PLASMA MULTIANALYTE PROFILING IN MILD COGNITIVE IMPAIRMENT AND ALZHEIMER DISEASE

**David A. Bennett, Chicago:** In an elegant targeted proteomics study of 3 cohorts with more than 1,000 subjects, Hu et al.[1] nominated several peripheral proteins associated with Alzheimer disease (AD).

There has long been an interest in identifying peripheral biomarkers for AD.[2] Technological approaches to quantifying the proteome continue to improve, allowing the characterization of nearly 10,000 proteins from a single sample with about half of the proteins coded by the human genome.[3] However, hurdles remain. First, experiences with the genome suggest there will be many false-positives that are not consistently replicated. Second, common diseases (e.g., cerebrovascular disease, Lewy body pathology) and other factors—including proteins—that promote resilience track with clinically and pathologically diagnosed AD.[4,5]

Even the most carefully designed AD case-control studies will identify proteins associated with other diseases and resilience. Finally, determining whether proteins are resident in the human brain is essential for understanding their role in promoting cognitive impairment or maintaining cognition. Interestingly, one protein (interleukin-3) identified in the 2 discovery cohorts was identified in a targeted proteomics analysis of the human brain.[5]

Further study is needed but the human proteome is ripe for identifying novel therapeutic targets and biomarkers for AD and other neurologic diseases.

**Author Response: William T. Hu, Atlanta; David Holtzman, St. Louis; Leslie Shaw, John Trojanowski, Philadelphia; Holly Soares, New London, CT:** We agree with Dr. Bennett that determining the biological significance of CSF and blood biomarkers associated with AD represents the next logical step in developing these biomarkers further towards eventual clinical application. Along with interleukin-3, C-reactive protein (CRP) was found to be associated with plaques[6] and higher CRP levels in successful cognitive aging individuals were recently linked to lower risks of dementia among their relatives.[7] The connection to brain proteomic changes has also been observed. For example, altered CSF levels of fatty acid binding protein in 2 groups of patients with AD has been found[8,9] and fatty acid binding protein showed region-specific alterations in proteomic studies of AD brains.[10] While we do not expect all biomarker changes in the blood and CSF to directly reflect pathologic changes in the brain, a direct or indirect connection between brain pathology and biomarkers provides a window into detrimental and neuroprotective activities at the cellular and synaptic levels. As replication is a significant challenge in targeted proteomic analysis (such as the work we presented) as well as mass spectrometry-based unbiased proteomic studies, we hope a tandem discovery-validation design will accelerate the discovery of correlated brain, CSF, and blood biomarkers.




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