Valproic Acid Monotherapy in Pregnancy and Major Congenital Malformations.

**BACKGROUND:** The use of valproic acid in the first trimester of pregnancy is associated with an increased risk of spina bifida, but data on the risks of other congenital malformations are limited. **METHODS:** We first combined data from eight published cohort studies (1565 pregnancies in which the women were exposed to valproic acid, among which 118 major malformations were observed) and identified 14 malformations that were significantly more common among the offspring of women who had received valproic acid during the first trimester. We then assessed the associations between use of valproic acid during the first trimester and these 14 malformations by performing a case–control study with the use of the European Surveillance of Congenital Anomalies (EUROCAT) antiepileptic-study database, which is derived from population-based congenital anomaly registries. Registrations (i.e., pregnancy outcomes with malformations included in EUROCAT) with any of these 14 malformations were compared with two control groups, one consisting of infants with malformations not previously linked to valproic acid use (control group 1), and one consisting of infants with chromosomal abnormalities (control group 2). The data set included 98,075 live births, stillbirths, or terminations with malformations among 3.8 million births in 14 European countries from 1995 through 2005. **RESULTS:** Exposure to valproic acid monotherapy was recorded for a total of 180 registrations, with 122 registrations in the case group, 45 in control group 1, and 13 in control group 2. As compared with no use of an antiepileptic drug during the first trimester (control group 1), use of valproic acid monotherapy was associated with significantly increased risks for 6 of the 14 malformations under consideration; the adjusted odds ratios were as follows: spina bifida, 12.7 (95% confidence interval [CI], 7.7 to 20.7); atrial septal defect, 2.5 (95% CI, 1.4 to 4.4); cleft palate, 5.2 (95% CI, 2.8 to 9.9); hypospadias, 4.8 (95% CI, 2.9 to 8.1); polydactyly, 2.2 (95% CI, 1.0 to 4.5); and craniosynostosis, 6.8 (95% CI, 1.8 to 18.8). Results for exposure to valproic acid were similar to results for exposure to other antiepileptic drugs. **CONCLUSIONS:** The use of valproic acid monotherapy in the first trimester was associated with significantly increased risks of several congenital malformations, as compared with no use of antiepileptic drugs or with use of other antiepileptic drugs.

Intrauterine Exposure to Carbamazepine and Specific Congenital Malformations: Systematic Review and Case-Control Study.

**OBJECTIVE:** To identify specific major congenital malformations associated with use of carbamazepine in the first trimester of pregnancy. **DESIGN:** A review of all published cohort studies to identify key indications and a population based case-control study to test these indications. **SETTING:** Review of PubMed, Web of Science, and Embase for papers about carbamazepine exposure in the first trimester of pregnancy and specific malformations, and the EUROCAT Antiepileptic Study Database, including data from 19 European population based congenital anomaly registries, 1995-2005. **PARTICIPANTS:** The literature review covered eight cohort studies of 2680 pregnancies with carbamazepine monotherapy exposure, and the EUROCAT dataset included 98 075 registrations of malformations covering over 3.8 million births. **MAIN OUTCOME MEASURES:** Overall prevalence for a major congenital malformation after exposure to carbamazepine monotherapy in the first trimester. Odds ratios for malformations with exposure to carbamazepine among cases (five types of malformation identified in the literature review) compared with two groups of controls: other non-chromosomal registrations of malformations and chromosomal syndromes. **RESULTS:** The literature review yielded an overall prevalence for a major congenital malformation of 3.3% (95% confidence interval 2.7 to 4.2) after...
exposure to carbamazepine monotherapy in the first trimester. In 131 registrations of malformations, the fetus had been exposed to carbamazepine monotherapy. Spina bifida was the only specific major congenital malformation significantly associated with exposure to carbamazepine monotherapy (odds ratio 2.6 (95% confidence interval 1.2 to 5.3) compared with no antiepileptic drug), but the risk was smaller for carbamazepine than for valproic acid (0.2, 0.1 to 0.6). There was no evidence for an association with total anomalous pulmonary venous return (no cases with carbamazepine exposure), cleft lip (with or without palate) (0.2, 0.0 to 1.3), diaphragmatic hernia (0.9, 0.1 to 6.6), or hypospadias (0.7, 0.3 to 1.6) compared with no exposure to antiepileptic drugs. Further exploratory analysis suggested a higher risk of single ventricle and atrioventricular septal defect. CONCLUSION: Carbamazepine teratogenicity is relatively specific to spina bifida, though the risk is less than with valproic acid. Despite the large dataset, there was not enough power to detect moderate risks for some rare major congenital malformations.

Commentary

The researchers in these two published reports used a fresh approach to an old dilemma, resulting in the addition of valuable detailed information about the specific structural teratogenic risks associated with the use of valproic acid (VPA) and of carbamazepine (CBZ) during the first trimester of pregnancy.

Most antiepileptic drug (AED) pregnancy registries prospectively follow a cohort of women on AEDs and record outcomes. Comparisons are usually made with a group of healthy control women without epilepsy and on no AEDs and occasionally with women on other AEDs. These traditional pregnancy registry studies have limited power to detect increased risk for specific, individual major congenital malformations (MCMs), as most occur quite rarely. A recent extensive evidence-based review of published studies, the Practice Parameter Update: Management of Women with Epilepsy—Focus on Pregnancy report from the American Academy of Neurology (AAN) and the American Epilepsy Society (AES), concluded that it is possible that valproate (VPA) as monotherapy and probably that VPA as part of polytherapy contribute to the development of MCMs compared with women without epilepsy who are untreated with AEDs (1). However, because the majority of the women with epilepsy require treatment during the childbearing years, it is more helpful to the clinician to differentiate risks among AEDs. The AAN/AES practice parameter update concluded that it is highly probable that intrauterine first-trimester VPA monotherapy exposure has a higher risk of MCMs compared with women on CBZ and possible compared with phenytoin or lamotrigine. For the appropriate epilepsy syndrome, this conclusion would favor the use of CBZ over VPA but falls short of providing the detailed information needed for adequate counseling when treating women with epilepsy who plan to become pregnant or during their pregnancy.

What clinicians and patients really want to know is not only the magnitude of the risk for any type of MCM, but what types of MCM are more likely to occur. MCMs are defined as an abnormality of an essential anatomical structure present at birth that interferes significantly with function or that requires major intervention. Not all MCMs are similar in severity, degree of intervention required, or in their impact on quality of life. For example, studies have demonstrated the devastating impact on a child born with spina bifida as well as on the entire family (2, 3). For specific MCMs, the AAN/AES practice parameter update was only able to conclude that VPA exposure probably contributes to neural tube defects (spina bifida) and facial clefts and possibly contributes to hypospadias. The conclusions for other AEDs were more limited: it is possible that CBZ contributes to posterior cleft palate, that phenobarbital contributes to cardiac malformations, and that phenytoin contributes to cleft palate (1). Although the association did not hold up in this the AAN/AES practice parameter update, previous smaller studies have raised the concern that CBZ could be linked to an increased risk of spina bifida.

These two studies by Jentink et al. employed a reverse approach by using 19 population-based registries of congenital anomalies from 14 countries, the European Surveillance of Congenital Anomalies (EUROCAT) antiepileptic-study database. The registries covered 3,881,592 live births and stillbirths in 1995 to 2005, with 98,075 births that involved an MCM. The investigators performed each study in two steps. For VPA, they first combined data from eight published studies to identify MCMs that may occur at a greater frequency than expected among offspring exposed to VPA during the first trimester. They identified 14 specific MCMs with a higher prevalence than in the EUROCAT reference group of 3.8 million. The investigators then conducted a population-based, case-control study to test their hypotheses, using the EUROCAT antiepileptic-study database. They compared the odds of exposure with VPA monotherapy among cases (for each of the 14 MCMs) with the odds of exposure in two groups of controls—a group with MCMs other than those under study and a group with MCMs associated with chromosomal abnormalities. The investigators went on to determine exposure to VPA monotherapy during the first trimester compared with the absence of exposure to AEDs and with exposure to an AED monotherapy other than VPA. They investigated the nearly identical approach for CBZ monotherapy, combining data from 8 cohort studies to identify MCMs that may occur at a greater frequency than expected.

For the case-control study of VPA using the EUROCAT antiepileptic-study database, pregnancies involving spina bifida had an adjusted odds ratio (OR) of 12.7 (CI: 7.7–20.7) for VPA exposure versus no AED exposure. Five other MCMs had significantly increased adjusted ORs of 2.2 to 6.8 (vs no AED): atrial septal defect, cleft palate, hypospadias, polydactyly, and...
craniosynostosis. Even more helpful to treating clinicians were the findings from comparisons with the other AED monotherapy regimens. The findings again showed a relative increase and were almost identical with the following two exceptions: the OR for craniosynostosis was no longer significantly increased in the VPA group, but the ventricular septal defect was increased in the VPA group. The adjusted OR for spina bifida and VPA exposure versus other AED monotherapy exposures was 5.7 (CI: 2.6–12.3).

For the CBZ analysis, five types of MCM were identified in the literature review and were considered indications to be tested in the case-control study. Based on an abstract report from the North American AED pregnancy registry, the authors decided to include the additional indication for the risk of cleft palate (4). For the case-control study of CBZ using the EUROCAT database, spina bifida was the only specific MCM significantly associated with exposure to CBZ monotherapy, with an OR of 2.6 (CI: 1.2–5.3) compared with nonchromosomal controls and 4.2 (CI: 1.5–11.2) compared with chromosomal controls. However, in the comparison for other AED monotherapies excluding VPA, exposure to CBZ showed no difference in the association with spina bifida, with an OR of 1.1 (CI: 0.4–3.6). There were differences when comparing directly with VPA monotherapy, with findings favorable for CBZ. The OR were significantly lower for CBZ compared with VPA exposure for spina bifida and for hypospadias. In contrast to other reports, the risk for isolated cleft palate and for cleft lip with or without palate was not higher in the CBZ monotherapy group compared with controls or other AEDs.

The remarkable finding is the consistency of a higher risk for MCMs for VPA echoed throughout several pregnancy studies around the world and now supported by a very different methodologic approach. These studies more clearly identify which MCMs are likely to occur with the use of VPA, including in comparison with other AEDs as a group and to CBZ in isolation. However, the one finding of an association of spina bifida with first-trimester CBZ use should also be considered when counseling women of childbearing age, especially given the severity and impact of this type of MCM. The findings from this research group further underscore the message that by choosing to prescribe any AED other than VPA, the clinician is automatically lowering the risk for future pregnancies. This should be a guiding principle when treating adolescent girls and women with epilepsy.

by Page B. Pennell, MD

References
Instructions

The purpose of this form is to provide readers of your manuscript with information about your other interests that could influence how they receive and understand your work. Each author should submit a separate form and is responsible for the accuracy and completeness of the submitted information. The form is in four parts.

1. Identifying information.
   Enter your full name. If you are NOT the main contributing author, please check the box “no” and enter the name of the main contributing author in the space that appears. Provide the requested manuscript information.

2. The work under consideration for publication.
   This section asks for information about the work that you have submitted for publication. The time frame for this reporting is that of the work itself, from the initial conception and planning to the present. The requested information is about resources that you received, either directly or indirectly (via your institution), to enable you to complete the work. Checking “No” means that you did the work without receiving any financial support from any third party – that is, the work was supported by funds from the same institution that pays your salary and that institution did not receive third-party funds with which to pay you. If you or your institution received funds from a third party to support the work, such as a government granting agency, charitable foundation or commercial sponsor, check “Yes”. Then complete the appropriate boxes to indicate the type of support and whether the payment went to you, or to your institution, or both.

3. Relevant financial activities outside the submitted work.
   This section asks about your financial relationships with entities in the bio-medical arena that could be perceived to influence, or that give the appearance of potentially influencing, what you wrote in the submitted work. For example, if your article is about testing an epidermal growth factor receptor (EGFR) antagonist in lung cancer, you should report all associations with entities pursuing diagnostic or therapeutic strategies in cancer in general, not just in the area of EGFR or lung cancer.

   Report all sources of revenue paid (or promised to be paid) directly to you or your institution on your behalf over the 36 months prior to submission of the work. This should include all monies from sources with relevance to the submitted work, not just monies from the entity that sponsored the research. Please note that your interactions with the work’s sponsor that are outside the submitted work should also be listed here. If there is any question, it is usually better to disclose a relationship than not to do so.

   For grants you have received for work outside the submitted work, you should disclose support ONLY from entities that could be perceived to be affected financially by the published work, such as drug companies, or foundations supported by entities that could be perceived to have a financial stake in the outcome. Public funding sources, such as government agencies, charitable foundations or academic institutions, need not be disclosed. For example, if a government agency sponsored a study in which you have been involved and drugs were provided by a pharmaceutical company, you need only list the pharmaceutical company.

4. Other relationships
   Use this section to report other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work.
American Epilepsy Society

Epilepsy Currents Journal
Disclosure of Potential Conflicts of Interest

Section #1 Identifying Information

1. Today's Date: __4/13/11_______________________________

2. First Name ___Page____________________      Last Name ___Pennell______________   Degree __MD_____

3. Are you the Main Assigned Author?  __X__  Yes      ____  No
   If no, enter your name as co-author ___________________________________________________

4. Manuscript/Article Title:____ The Devil Is in the Details: Not All AED-Associated Major Congenital Malformations Are Equal_______________________________________________________________

5. Journal Issue you are submitting for:  _____??____________________________________________________

Section #2 The Work Under Consideration for Publication

Did you or your institution at any time receive payment or services from a third party for any aspect of the submitted work (including but not limited to grants, data monitoring board, study design, manuscript preparation, statistical analysis, etc.)?

Complete each row by checking “No” or providing the requested information. If you have more than one relationship just add rows to this table.

<table>
<thead>
<tr>
<th>Type</th>
<th>No</th>
<th>Money Paid to You</th>
<th>Money to Your Institution*</th>
<th>Name of Entity</th>
<th>Comments**</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Grant</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Consulting fee or honorarium</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Support for travel to meetings for the study or other purposes</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. Fees for participating in review activities such as data</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>monitoring boards, statistical analysis, end point committees,</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>and the like</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. Payment for writing or reviewing the manuscript</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6. Provision of writing assistance, medicines, equipment, or</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>administrative support.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7. Other</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*  This means money that your institution received for your efforts on this study.
**  Use this section to provide any needed explanation.
### Section #3 Relevant financial activities outside the submitted work.

Place a check in the appropriate boxes in the table to indicate whether you have financial relationships (regardless of amount of compensation) with entities as described in the instructions. Use one line for each entity; add as many lines as you need by clicking the “Add” box. You should report relationships that were present during the 36 months prior to submission.

Complete each row by checking “No” or providing the requested information. If you have more than one relationship just add rows to this table.

<table>
<thead>
<tr>
<th>Type of relationship (in alphabetical order)</th>
<th>No</th>
<th>Money Paid to You</th>
<th>Money to Your Institution*</th>
<th>Name of Entity</th>
<th>Comments**</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Board membership</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Consultancy</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Employment</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. Expert testimony</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. Grants/grants pending</td>
<td></td>
<td>X</td>
<td>NIH, Centers for Disease Control, Epilepsy Foundation, Milken Family Foundation, UCB Pharma, GlaxoSmithKline, Marinus Pharmaceuticals</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6. Payment for lectures including service on speakers bureaus</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7. Payment for manuscript preparation.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8. Patents (planned, pending or issued)</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9. Royalties</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10. Payment for development of educational presentations</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11. Stock/stock options</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12. Travel/accommodations/meeting expenses unrelated to activities listed.**</td>
<td>X</td>
<td>American Epilepsy Society, Epilepsy Foundation, National Epifellows, Albany Medical College</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>13. Other (err on the side of full disclosure)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* This means money that your institution received for your efforts.

** For example, if you report a consultancy above there is no need to report travel related to that consultancy on this line.

### Section #4 Other relationships
Are there other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work?

___ No other relationships/conditions/circumstances that present a potential conflict of interest.
___ Yes, the following relationships/conditions/circumstances are present:

______________________________________________________________________________________________
______________________________________________________________________________________________
______________________________________________________________________________________________

Thank you for your assistance.

*Epilepsy Currents* Editorial Board