### Commentary

Approximately one-quarter of patients with active epilepsy are females of childbearing age, necessitating treatment with medications that are known teratogens during this vulnerable life stage. However, most women with epilepsy require chronic treatment with an antiepileptic drug (AED) to maintain seizure control. Pregnancy registries over the last 2 decades have provided incremental advances in our knowledge quantifying the teratogenic risks, but the most useful information to the prescribing clinician is findings that delineate differential risks amongst the AEDs. Several pregnancy registries consistently report that of the AEDs analyzed thus far, valproic acid has the highest risk for major congenital malformations (MCM) and poor neurodevelopmental outcomes (1–3). The AAN/AES practice parameter update concluded that it is highly probable that intrauterine first-trimester valproic acid monotherapy exposure has a higher risk of MCMs compared with carbamazepine and possibly compared with phenytoin or lamotrigine (1). However, evidence necessary to direct the care of women with epilepsy planning and during pregnancy is still inadequate, with AED-specific risk profiles for many of the medications still unknown.

Most AED pregnancy registries prospectively follow a cohort of women on AEDs across several sites and record outcomes. Given the low incidence of MCMs (1.6–2.1% in the general population and 4–8% in women with epilepsy on AED monotherapies [4]), it is difficult to gain enough statistical power to ascertain differential risks between different doses for the same drug or between dose ranges of different drugs.
The one exception is for valproic acid, with findings from several studies supporting an association between dose and risk of MCMs (5, 6). One study also reported a dose-associated risk for lamotrigine (3), but another study did not find an effect of maximal first-trimester dose level despite a large number of outcomes (7). It is less clear if there is a dose-related risk for other AEDs.

EURAP (An International Registry of Antiepileptic Drugs and Pregnancy) is an observational cohort study with sites spanning 42 countries, generating outcomes for a large number of pregnancies. Of the eligible pregnancy outcomes, 86% were exposed to one of four common AEDs (carbamazepine, lamotrigine, valproic acid, phenobarbital). The rate of MCMs with lamotrigine <300 mg/d was so low (2.0%, 95% confidence interval [CI]: 1.19–3.24), that it was used as the comparator for other lamotrigine doses and other AEDs at various doses. This modest rate of MCMs is not unlike rates published from other AED pregnancy registries that included all lamotrigine doses, with 1.9% (95% CI: 1.3–2.8) MCM rate in the North American AED Registry. Compared with lamotrigine <300 mg/d, MCM rates were higher for valproic acid and phenobarbital at all doses and for carbamazepine at doses >400 mg/d (odds ratios [OR] of 2.5–16); for each AED, the OR increased with the higher dose ranges. MCM rates were modestly low for carbamazepine <400 mg/d (3.4%, 95% CI: 1.11–7.71) similar to other registry findings (1), but with fairly wide confidence intervals. Other notable findings were the high overall MCM rate (24%) and the neural-tube defects rate (2%) for valproic acid >1,500 mg/d.

Perhaps the most novel results are the significantly higher odds ratios for MCMs across all the drugs studied with internal daily dose range comparisons: carbamazepine (≥1,000 vs <400 mg/d; OR, 2.9; 95% CI: 1.04–8.0), lamotrigine (≥300 vs <300 mg/d; OR, 2.2; 95% CI: 1.12–4.35), phenobarbital (≥150 vs <150 mg/d; OR, 3.2; 95% CI: 1.11–9.45), valproic acid (≥700 to <1,500 vs <700 mg/d; OR, 2.1; 95% CI: 1.25–3.43), valproic acid (≥1,500 vs <700 mg/d; OR, 5.8; 95% CI: 3.07–10.92).

The AED doses utilized in this study were specific to the time of conception. This study did not take into account any subsequent dosage changes, and thus this is not an analysis of dose or level of exposure throughout pregnancy or even the first trimester. These findings should not be extrapolated to maintaining the lowest daily doses studied throughout pregnancy (phenobarbital <150 mg, carbamazepine <400 mg, lamotrigine <300 mg, and valproic acid <700 mg). Drug clearance markedly increases for many AEDs during pregnancy, and dosage adjustments are necessary to avoid seizure worsening (9). This is especially true for AEDs that have markedly increased clearance during pregnancy such as lamotrigine (10). Uncontrolled seizures have been associated with fetal loss, fetal hypoxia, and even poor neurodevelopment (11). Women with active epilepsy need not only effective treatments but effective management of their AEDs during pregnancy to optimize maternal and fetal outcomes. Tomson et al. reported on the percentage of women that were seizure free throughout pregnancy, and similar ranges of 62 to 71 percent were seen for all AEDs. However, the authors correctly emphasize that this is not a direct comparison, as patient groups differed in seizure types and severity at baseline, thus dictating their specific AED type and dose entering pregnancy.

This analysis of outcomes by type of AED monotherapy and by dose of AED at time of conception offers important information for management of women with epilepsy during the entire span of childbearing years. Clinicians cannot wait until the diagnosis of pregnancy to determine the optimal lowest dose for the individual patient. Nor should they wait until the patient’s decision to become pregnant as 50% of pregnancies are unplanned in women with epilepsy (12). However, if a patient does decide to stop an estrogen-containing contraceptive, this provides a window of opportunity to lower fetal risk by adjusting the AED dose downward if she is on an AED with a metabolic route that is induced by estrogens (for example, lamotrigine, valproic acid).

The general principle that teratogens act in a dose-dependent manner for MCMs likely holds true for other effects of in utero AED exposure such as brain development. The Neurodevelopmental Effects of Antiepileptic Drugs (NEAD) study group reported that performance at 3 years old was negatively associated with maternal valproic acid dose for both verbal and nonverbal abilities and negatively associated with carbamazepine dose for verbal abilities (2). Future research should include other fetal outcomes such as neurodevelopment and intrauterine growth as well as maternal outcomes of seizure control and obstetric complications. Dose is only a surrogate marker of fetal exposure, especially with the variability that occurs with clearance alterations during pregnancy. Studies, ideally, would include serum concentrations of mother and newborn and key phenotype, pharmacodynamic, and pharmacogenetic factors, with the ultimate goal of a personalized profile that balances maternal health and fetal exposure risk throughout pregnancy.

In summary, this report from EURAP provides another important incremental advance in the management of women with epilepsy during the reproductive years; the clinician should not only consider AED type but also daily dose. Too complicated? Not really, as the message is so simple.

by Page B. Pennell, MD

References


American Epilepsy Society

Epilepsy Currents Journal

Disclosure of Potential Conflicts of Interest

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 (DGFR) 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: 03.21.12

2. First Name Page Last Name Pennell Degree MD

3. Are you the Main Assigned Author? ☑ Yes ☐ No

If no, enter your name as co-author:

4. Manuscript/Article Title: Too Complicated or So Simple:,

5. Journal Issue you are submitting for: 12.2

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>☑</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Consulting fee or honorarium</td>
<td>☑</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>☑</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. Fees for participating in review activities such as data</td>
<td>☑</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>☑</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6. Provision of writing assistance, medicines, equipment, or</td>
<td>☑</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>☑</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>☒</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Consultancy</td>
<td>☒</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Employment</td>
<td>☒</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. Expert testimony</td>
<td>☒</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. Grants/grants pending</td>
<td></td>
<td>yes</td>
<td></td>
<td>NIH, EF, Milken Family Foundation</td>
<td></td>
</tr>
<tr>
<td>6. Payment for lectures including service on speakers bureaus</td>
<td></td>
<td>yes</td>
<td></td>
<td>CME grand rounds at Albany Medical college, SUNY downstate, NE regional epilepsy centers</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></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9. Royalties</td>
<td>☒</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10. Payment for development of educational presentations</td>
<td>☒</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11. Stock/stock options</td>
<td>☒</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12. Travel/accommodations/meeting expenses unrelated to activities listed.**</td>
<td></td>
<td>yes</td>
<td></td>
<td>EF, AES, NIH</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