SPECIAL ARTICLE

Practice Parameter update: Management issues for women with epilepsy—Focus on pregnancy (an evidence-based review): Teratogenesis and perinatal outcomes

Report of the Quality Standards Subcommittee and Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology and American Epilepsy Society

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ABSTRACT

Objective: To reassess the evidence for management issues related to the care of women with epilepsy (WWE) during pregnancy.

Methods: Systematic review of relevant articles published between January 1985 and June 2007.

Results: It is highly probable that intrauterine first-trimester valproate (VPA) exposure has higher risk of major congenital malformations (MCMs) compared to carbamazepine and possible compared to phenytoin or lamotrigine. Compared to untreated WWE, it is probable that VPA as part of polytherapy and possible that VPA as monotherapy contribute to the development of MCMs. It is probable that antiepileptic drug (AED) polytherapy as compared to monotherapy regimens contributes to the development of MCMs and to reduced cognitive outcomes. For monotherapy, intrauterine exposure to VPA probably reduces cognitive outcomes. Further, monotherapy exposure to phenytoin or phenobarbital possibly reduces cognitive outcomes. Neonates of WWE taking AEDs probably have an increased risk of being small for gestational age and possibly have an increased risk of a 1-minute Apgar score of <7.

Recommendations: If possible, avoidance of valproate (VPA) and antiepileptic drug (AED) polytherapy during the first trimester of pregnancy should be considered to decrease the risk of major congenital malformations (Level B). If possible, avoidance of VPA and AED polytherapy throughout pregnancy should be considered to prevent reduced cognitive outcomes (Level B). If possible, avoidance of phenytoin and phenobarbital during pregnancy may be considered to prevent reduced cognitive outcomes (Level C). Pregnancy risk stratification should reflect that the offspring of women with epilepsy taking AEDs are probably at increased risk for being small for gestational age (Level B) and possibly at increased risk of 1-minute Apgar scores of <7 (Level C). *Neurology*® 2009;73:133–141

GLOSSARY

AAN = Academy of Neurology; **AED** = antiepileptic drug; **CBZ** = carbamazepine; **CI** = confidence interval; **LTG** = lamotrigine; **MCM** = major congenital malformation; **OR** = odds ratio; **PB** = phenobarbital; **PHT** = phenytoin; **RR** = relative risk; **SGA** = small for gestational age; **VPA** = valproate; **WWE** = women with epilepsy.

Recent estimates of the US population[1] and the prevalence of epilepsy[2] indicate that approximately one-half million women with epilepsy (WWE) are of childbearing age. It has also been estimated that three to five births per thousand will be to WWE.[3] Epilepsy is defined by the presence of recurrent, unprovoked seizures, and the treatment is typically a daily, long-term antiepileptic drug (AED) regimen. The majority of people with epilepsy have well-controlled seizures, are otherwise healthy, and therefore expect to participate fully in life experiences, including childbearing.

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The Mission Statements of the Quality Standards Subcommittee (QSS) and Therapeutics and Technology Assessment (TTA) Subcommittee, Conflict of Interest Statement, QSS members, TTA members, AAN classification of evidence, Classification of recommendations (appendices e-1 through e-5), as well as references e1 through e5 and tables e-1 through e-7, are available on the *Neurology*® Web site at www.neurology.org.

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This parameter summarizes evidence for three important issues regarding the clinical management of WWE who are pregnant or plan pregnancy:

1. What is the risk of major congenital malformations (MCMs) associated with intrauterine exposure to AEDs in neonates born to WWE?
2. What is the risk of adverse long-term cognitive outcomes in children born to WWE?
3. What is the risk of death, low birthweight, and low Apgar scores in neonates born to WWE?

DESCRIPTION OF THE ANALYTIC PROCESS

The panel formation, literature search strategy, and literature analytic process are described in the companion article.[4]

ANALYSIS OF EVIDENCE

Major congenital malformations. Fifty-two relevant articles were identified by the literature search. Articles were classified for risk of bias using American Academy of Neurology (AAN) criteria for classification of evidence for causality (appendix e-4A on the *Neurology*® Web site at www.neurology.org). Studies rated Class III or higher that contributed to conclusions are summarized in tables e-1 through e-5.

MCMs were defined as structural abnormalities with surgical, medical, or cosmetic importance.[5] Minor malformations such as facial dysmorphism were not considered in the statistical analysis. For the purpose of this parameter, the presence of MCMs was considered an objective outcome. To attain a Class I or II rating, the study must have accounted for confounding by maternal age and socioeconomic status.

The contribution of maternal epilepsy to the risk of MCMs is not specifically considered herein, since the evidence is unclear and the risk, if any, appears small.[6] However, it cannot be stated that the risk imparted by maternal epilepsy is zero. Therefore, we addressed the question regarding risk of MCMs due to AEDs taken during the first trimester by including only studies where WWE not taking AEDs served as comparators. We acknowledge that the severity of the maternal epilepsy in terms of seizure type and frequency cannot be completely matched between comparator groups and may contribute to the difference in outcomes in the two groups. Women without epilepsy who were taking AEDs for other reasons were not included.

For the subsequent questions, the evaluation is focused on the risks of AEDs compared to each other, or findings specific to an individual AED such as a dose-malformation relationship. Therefore, three studies used in answering these questions[7-9] include the offspring of mothers who took AEDs for various indications.

Do AEDs taken during the first trimester of pregnancy increase the risk of MCMs in the offspring of WWE compared to the offspring of WWE not on AEDs?

AEDs in general. One Class I study[10] showed no increased risk of MCMs in the offspring of WWE taking AEDs compared to the offspring of WWE not taking AEDs (relative risk [RR] 1.19, confidence interval [CI] 0.59–2.40). However, the study was insufficiently sensitive to exclude a substantially increased risk. Two Class II studies (odds ratio [OR] 3.92, CI 1.29–11.90,[5] and OR 1.70, CI 1.07–2.68)[11] found increased risks of MCMs with maternal AED exposure compared to untreated WWE.

Valproate. One Class II study[11] demonstrated increased risk of MCMs in the offspring of WWE using valproate (VPA) in monotherapy (OR 4.18, CI 2.31–7.57) or polytherapy (OR 3.54, CI 1.42–8.11). One Class I study[10] also showed the risk of MCMs with polytherapy including VPA was increased compared to untreated WWE (RR 2.52, CI 1.17–5.44).

Carbamazepine. One Class I study[10] found no increased risk of MCMs in the offspring of WWE taking carbamazepine (CBZ) (RR 0.63, CI 0.28–1.41).

Lamotrigine. One Class I study[10] observed no increased risk of MCMs in the offspring of WWE taking lamotrigine (LTG) (RR 0.92, CI 0.41–2.05) but was insufficiently sensitive to exclude a substantially increased risk.

The absolute risk of MCMs in the largest Class I study[10] with at least 80 outcomes per AED is as follows: CBZ (n = 900) 2.2% (CI 1.4–3.4), VPA (n = 715) 6.2% (CI 4.6–8.8), LTG (n = 647) 3.2% (CI 2.1–4.9), phenytoin (PHT) (n = 82) 3.7% (CI 1.3–10.2).

Conclusions

- AEDs taken during the first trimester probably increase the risk of MCMs in the offspring of WWE (two adequately sensitive Class II studies) but it cannot be determined if the increased risk is imparted from all AEDs or from only one or some AEDs.
- VPA monotherapy during the first trimester possibly increases the risk of MCMs in the offspring of WWE (one Class II study).
- VPA used in polytherapy probably increases the risk of MCMs in the offspring of WWE (one Class I study).
- CBZ probably does not substantially increase the risk of MCMs in the offspring of WWE (one Class I study).
- There is insufficient evidence to determine if LTG (one inadequately sensitive Class I study) or other specific AEDs (no Class III or better evidence) increase the risk of MCMs in the offspring of WWE.

Recommendations

- Although there is evidence that AEDs taken during the first trimester probably increase the risk of MCMs in the offspring of WWE, it cannot be determined if the increased risk is imparted from all AEDs or from only one or some AEDs. Therefore, no recommendation is made from this conclusion.
- If possible, avoidance of the use of VPA as part of polytherapy during the first trimester of pregnancy should be considered to decrease the risk of MCMs (Level B).
- If possible, avoidance of the use of VPA monotherapy during the first trimester of pregnancy may be considered to decrease the risk of MCMs (Level C).

Is exposure to a specific AED during the first trimester of pregnancy associated with an increased risk of MCMs compared to exposure to other AEDs? Two Class I studies (OR 2.97, CI 1.65–5.35,[10] and OR 2.51, CI 1.43–4.86)[7] revealed that VPA monotherapy is associated with a greater risk for MCMs than CBZ monotherapy.

One Class I study[10] and one Class II study[11] showed that VPA as part of polytherapy was associated with greater risk than polytherapy without VPA (OR 2.49, CI 1.31–4.70,[10] and OR 1.97, CI 0.58–6.66[11]).

One Class II study[12] showed that VPA is associated with a greater risk than PHT (OR 9.06, CI 1.13–72.14).

We performed comparisons for three of the four Class III studies, using primary data from the articles.[13-15] All significant comparisons between AEDs are reported herein. In two Class III studies,[13,14] VPA was associated with increased risk when individually compared to CBZ (RR 4.34, CI 1.79–10.53[13] and RR 3.83, CI 1.41–10.39)[14] and LTG (RR 5.58, CI 2.06–15.09[13] and RR 17.04, CI 2.27–128.05).[14] The third Class III study[15] showed VPA was associated with greater risk than phenobarbital (PB) (RR 5.66, CI 1.19–26.88).

All four Class III studies showed VPA was associated with greater risk than all other monotherapies combined. We compared VPA to CBZ, LTG, and PHT in two studies and found increased risk in both (RR 5.6, CI 2.42–12.92,[13] and RR 4.59, CI 2.07–10.18).[14] In the third Class III study,[15] we compared VPA to PB, CBZ, PHT, and primidone and found increased risk (RR 3.25, CI 1.27–8.33). In the fourth Class III study, we found increased risk of VPA compared to three undisclosed AEDs (OR 4.0, CI 2.1–7.4).[16]

Conclusions

- It is highly probable that taking VPA monotherapy during the first trimester of pregnancy contributes to the development of MCMs in the offspring of WWE compared to taking CBZ (two Class I studies).
- VPA as part of polytherapy in the first trimester of pregnancy probably contributes to the development of MCMs in the offspring of WWE compared to polytherapy that does not include VPA (one Class I study).
- Taking VPA during the first trimester of pregnancy possibly contributes to the development of MCMs in the offspring of WWE compared to taking PHT (one Class II study).
- Taking VPA during the first trimester of pregnancy possibly contributes to the development of MCMs in the offspring of WWE compared to taking LTG (two Class III studies).

Recommendations

- To reduce the risk of MCMs, the use of VPA during the first trimester of pregnancy should be avoided, if possible, compared to the use of CBZ (Level A).
- To reduce the risk of MCMs, avoidance of the use of polytherapy with VPA during the first trimester of pregnancy, if possible, should be considered, compared to polytherapy without VPA (Level B).
- To reduce the risk of MCMs, avoidance of the use of VPA during the first trimester of pregnancy, if possible, may be considered, compared to the use of PHT or LTG (Level C).

Is the risk of MCMs greater for AED polytherapy compared to AED monotherapy when taken during the first trimester of pregnancy? One Class I study[10] showed a moderately increased risk of MCMs with polytherapy vs monotherapy (RR 1.62, CI 1.14–2.31). Three Class II studies (OR 1.76, CI 0.94–3.31[11]; OR 2.00, CI 0.80–3.74[5]; and OR 1.46, CI 0.83–2.56)[12] demonstrated no increased risk with polytherapy. However, these studies were insufficiently sensitive to exclude a substantially increased risk.

Conclusion. Polytherapy probably contributes to the development of MCMs in the offspring of WWE as compared to monotherapy (one Class I study).

Recommendation. To reduce the risk of MCMs, avoidance of the use of AED polytherapy during the first trimester of pregnancy, if possible, compared to monotherapy should be considered (Level B).

Is there a relationship between AED dose and the risk of MCMs in the offspring of WWE? All studies evaluated AED dose in the first trimester and MCMs. In one Class I study,[10] a relationship between AED dose and risk of MCMs was reported for LTG but not VPA. Using the Cochran Armitage method,[17] we

found a significant dose relationship with VPA (exact tests one-sided $p = 0.02$, two-sided $p = 0.04$) and with LTG (exact tests one-sided $p = 0.01$, two-sided $p = 0.02$), but not with CBZ (exact tests one-sided $p = 0.19$, two-sided $p = 0.31$). Two Class II studies[11,12] and six Class III studies[13-15,18-20] also found a relationship between VPA dose and MCMs. The VPA dose above which MCMs were significantly more likely to occur was not consistent, but was approximately 1,000 mg daily in five studies.[12,13,18-20]

Conclusion. There is probably a relationship between the dose of VPA and LTG and the risk of development of MCMs in the offspring of WWE (one Class I study).

Recommendation. Limiting the dosage of VPA or LTG during the first trimester, if possible, should be considered to lessen the risk of MCMs (Level B).

Are there specific MCMs associated with specific AEDs? One Class I study[10] showed increased risk of neural tube defects and facial clefts with VPA (RR 5.32, CI 1.38–20.50 for neural tube defects and RR 4.18, CI 1.55–11.25 for facial clefts). One Class II study[8] showed increased risk for cleft palate with PHT and posterior cleft palate with CBZ. Another Class II study[12] showed increased risk of neural tube defects and hypospadias with VPA. Two Class III studies showed increased risk of spina bifida with VPA,[9,21] and one showed increased risk of hypospadias.[9] Two Class III studies[9,15] showed increased risk of cardiac malformations associated with PB.

Conclusions

- PHT exposure in utero possibly contributes to the risk of cleft palate (one Class II study).
- CBZ exposure in utero possibly contributes to the risk of posterior cleft palate (one Class II study).
- VPA exposure in utero probably contributes to neural tube defects and facial clefts (one Class I study) and possibly contributes to hypospadias (one Class II study).
- PB exposure in utero possibly contributes to cardiac malformations (two Class III studies).

Recommendations

- Avoidance of the use of VPA, if possible, should be considered to reduce the risk of neural tube defects and facial clefts (Level B) and may be considered to reduce the risk of hypospadias (Level C).
- Avoidance of PHT, CBZ, and PB, if possible, may be considered to reduce the risk of specific MCMs: cleft palate for PHT use, posterior cleft palate for CBZ use, and cardiac malformations for PB use (Level C).

Cognitive teratogenesis. Thirteen relevant articles were identified by the literature search (table e-6). These were rated for risk of bias using the AAN causality evidence classification scheme (appendix e-4A).

The outcome measure was an assessment of the child's IQ at age 2 years or older. Because maternal IQ has an important influence on child IQ,[22] studies were downgraded if they did not control for maternal IQ. Unlike the analysis for MCM risk, the cognitive risk related to AED exposure was not confined to the first trimester, since risk due to exposure may be present throughout pregnancy, as suggested by the literature.[23]

Is cognitive outcome reduced in children of WWE who are not exposed to AEDs in utero? Two Class II studies[24,25] observed that cognition is not reduced in children of WWE unexposed to AEDs. One was a blinded observational study[24] comparing the IQ of 64 children of WWE not taking AEDs with 121 controls. No important differences in IQ were found. The other study[25] showed no difference in the IQ of 57 children of untreated WWE and 57 control children matched for age, race, and socioeconomic status.

Conclusion. Cognition is probably not reduced in children of WWE who are not exposed to AEDs in utero (two Class II studies).

Recommendation. Counseling of WWE who are contemplating pregnancy should reflect that there is probably no increased risk of reduced cognition in the offspring of WWE not taking AEDs (Level B).

Is cognition reduced in children of WWE exposed to AEDs in utero? ***AEDs in general.*** Two Class II studies[26,27] and one Class III study[28] showed reduced cognition in the children of WWE on AEDs. One Class II study[29] and one Class III study[30] showed no reduction. The outcome measures for the studies included IQ testing, development quotient testing, or an assessment of developmental milestones. Differences across studies are likely due to variance in design and inadequate control for confounding factors.

Carbamazepine. Two Class II studies[24,31] and three Class III studies[30,32,33] showed CBZ does not increase the risk of poor cognitive outcomes compared to unexposed controls.

Valproate. Two Class II studies[24,31] showed VPA poses an increased risk of poor cognitive outcomes compared to unexposed controls.

Phenytoin. One Class II study[34] and two Class III studies[30,33] showed PHT poses an increased risk for poor cognitive outcomes compared to unexposed controls.

Phenobarbital. Two Class III cohorts (analyzed separately in a single report) of adult men exposed in utero to PB found reduced cognitive abilities compared to normative populations.[23]

Conclusions

- There is insufficient evidence to determine if the children of WWE on AEDs in general are at increased risk for reduced cognition (conflicting Class II studies).
- CBZ probably does not increase poor cognitive outcomes compared to unexposed controls (two Class II studies).
- VPA is probably associated with poor cognitive outcomes compared to unexposed controls (two Class II studies).
- PHT is possibly associated with poor cognitive outcomes compared to unexposed controls (one Class II and two Class III studies).
- PB is possibly associated with poor cognitive outcomes in male offspring of WWE compared to unexposed controls (two Class III studies).

Recommendations

- CBZ exposure probably does not produce cognitive impairment in offspring of WWE (Level B).
- Avoiding VPA in WWE during pregnancy, if possible, should be considered to reduce the risk of poor cognitive outcomes (Level B).
- Avoiding PHT in WWE during pregnancy, if possible, may be considered to reduce the risk of poor cognitive outcomes (Level C).
- Avoiding PB in WWE during pregnancy, if possible, may be considered to reduce the risk of poor cognitive outcomes (Level C).

Does AED polytherapy exposure during pregnancy pose an increased risk for poor cognitive outcome compared to monotherapy? Three Class II studies[24,26,35] showed that cognitive outcomes are reduced in children exposed to AED polytherapy compared to monotherapy. Outcome assessments included IQ, verbal IQ, and the Columbia Mental Maturity Scale.

Conclusion. Cognitive outcomes are probably reduced in children exposed to AED polytherapy as compared to monotherapy in utero (three Class II studies).

Recommendation. Monotherapy should be considered in place of polytherapy, if possible, for WWE who take AEDs during pregnancy to reduce the risk of poor cognitive outcomes (Level B).

Is exposure to a specific AED in utero associated with poor cognitive outcomes compared to other AEDs? ***Valproate.*** Two Class II studies[24,31] demonstrated reduced cognitive outcomes in children exposed to VPA during pregnancy compared to children exposed to CBZ. In one of the studies, the risk was also greater than that of PHT.[31]

Other AEDs. There was no evidence rated Class III or higher regarding other AEDs.

Conclusions

- Cognitive outcomes are probably reduced in children exposed to VPA during pregnancy compared to CBZ (two Class II studies).
- Cognitive outcomes are possibly reduced in children exposed to VPA during pregnancy compared to PHT (one Class II study).

Recommendations

- For WWE who are pregnant, avoidance of VPA, if possible, should be considered compared to CBZ to reduce the risk of poor cognitive outcomes (Level B).
- For WWE who are pregnant, avoidance of VPA, if possible, may be considered compared to PHT to reduce the risk of poor cognitive outcomes (Level C).

Adverse perinatal outcomes. Thirteen relevant articles were identified by the literature search (table e-7). Articles were rated for risk of bias using the AAN prognostic classification of evidence scheme (appendix e-4B).

The outcomes evaluated included 1) small for gestational age (SGA), defined as birthweight below the 10th percentile for the study population when adjusted for gestational age and gender; 2) perinatal death; and 3) Apgar scores.

Is there an increased risk of SGA outcomes in neonates born to WWE? Two Class II studies[36,37] showed increased risk of SGA for offspring of WWE taking AEDs. In one Class II study, pregnancies to WWE taking AEDs had more than twice the risk of SGA outcomes (n = 87) (OR 2.3, CI 1.3–4.0).[36] Pregnancies to WWE not taking AEDs did not show a significantly increased risk of SGA (OR 1.6, CI 0.9–2.6). However, the study was insufficiently sensitive to exclude a substantially increased risk.

Another Class II study[37] observed twice the risk of SGA in pregnancies of WWE taking AEDs compared to controls (n = 127) (OR 2.16, CI 1.34–3.47, absolute risk 17.3%). The authors found no increased risk for SGA in the offspring of WWE not taking AEDs.

Conclusion. Neonates of WWE taking AEDs probably have an increased risk of SGA of about twice the expected rate (two Class II studies).

Recommendation. Pregnancy risk stratification should reflect that the offspring of WWE taking AEDs during pregnancy probably have an increased risk of SGA. Further, AED use in WWE during pregnancy

should be considered in the differential diagnosis of SGA in their offspring (Level B).

Is there an increased risk of perinatal death in neonates born to WWE? Two Class II[38,39] studies observed no increased risk of perinatal death (OR 0.57, CI 0.18–1.77).[39] The studies were insufficiently sensitive to exclude a moderately increased risk.

Conclusion. There is probably no substantially increased risk of perinatal death in neonates born to WWE (two Class II studies).

Recommendation. Pregnancy risk stratification should reflect that neonates born to WWE probably do not have a substantially increased risk of perinatal death (Level B).

Are Apgar scores lower in neonates born to WWE? One Class II study[37] showed increased risk of 1-minute Apgar scores of <7 for WWE taking AEDs (n = 127) (OR 2.29, CI 1.29–4.05, absolute risk 11.0%). Further, this study showed increased rate of neonatal intensive care unit admission for neonates born to WWE taking AEDs. These two outcomes were not increased for the offspring of WWE not taking AEDs. Two Class III studies[40,e1] showed lowered Apgar scores compared to controls and three Class III studies[38,39,e2] did not. None of these Class III studies reported point estimates of comparative risks.

Conclusion. Neonates of WWE taking AEDs possibly have an increased risk of 1-minute Apgar scores of <7 of about twice the expected rate (one Class II study).

Recommendation. Pregnancy risk stratification should reflect that the offspring of WWE taking AEDs during pregnancy possibly have an increased risk of 1-minute Apgar scores of <7. Further, AED use in WWE during pregnancy may be considered in the differential diagnosis of a 1-minute Apgar score of <7 in their offspring (Level C).

Other perinatal outcomes such as respiratory distress, intrauterine growth retardation, and neonatal intensive care unit admission did not have adequate data to make conclusions.

CLINICAL CONTEXT This parameter focuses on the pregnancy-related risks of AEDs. However, it does not evaluate the risks of not taking AEDs during pregnancy. The seizure-prevention benefits of taking AEDs are clear for the nonpregnant patient and these same benefits apply for the pregnant patient and extend to the protection of the fetus from maternal seizures. Although many of the recommendations in this parameter suggest minimizing AED exposure during pregnancy, for most WWE, discontinuing AEDs is not a reasonable or safe option. Although the risks of seizures during pregnancy have not been systematically studied, discontinuing AEDs may expose the mother and fetus to physical injury from accidents arising from partial or generalized seizures. Decision pathways to assist in deciding when to discontinue AEDs are available.[e3]

Based upon the evidence reviewed, it seems reasonable to switch WWE of childbearing potential to a less teratogenic regimen when possible. The use of VPA is a particular dilemma. While VPA is an effective AED,[e4] it emerges as the AED with the greatest number of data showing an association with risk from in utero exposure. If the change from VPA to another AED is planned, it seems prudent to do this well before pregnancy to make sure the new treatment adequately prevents seizures. Changing to another AED during pregnancy poses risk of allergy, other serious adverse reactions, and polytherapy exposure. Once a patient is pregnant, changing from VPA several weeks into gestation will not avoid the risk of MCMs, since this phenomenon occurs very early in pregnancy. This may also apply to cognitive teratogenesis, since the timing of exposure related to this adverse outcome is unknown.

For many AEDs, in particular the newer AEDs, there were too few patients in the studies to make conclusions, and the teratogenicity of these drugs is unknown.

The finding that some MCMs occur more frequently with specific AED exposure needs to be viewed in context. MCMs seen more frequently with VPA, such as neural tube defects, can also be present with exposure to other AEDs, demonstrating that this is not an AED-specific MCM. Like other teratogens, AEDs as a teratogenic category produce a pattern of MCMs with overlap among the individual AEDs.

RECOMMENDATIONS FOR FUTURE RESEARCH Although this parameter answers some questions, it raises others that make this clinical situation even more challenging. The parameter shows an increased risk of MCMs with VPA exposure, but there is a paucity of specific information about the absolute risk of most other AEDs. This is particularly true for the newer AEDs, several of which are reasonable alternatives to VPA. With ongoing data submission to AED pregnancy registries, it is hoped that this information will soon be forthcoming.

The existence of an AED dose-malformation relationship needs to be clarified for all AEDs, with the incorporation of serum levels as well. Adverse neonatal outcomes and long-term cognitive outcomes of children exposed to AEDs in utero for both the older and newer AEDs need further clarification, as do the

short-term and long-term cognitive risks of AED exposure in the neonatal and infantile periods through breastfeeding.

In addition, future research should begin to evaluate metabolic systems for which modification could lower teratogenic risk, such as glutathione reductase, superoxide dismutase, epoxide hydrolase, and other toxin-scavenging mechanisms. Further, the interactions between AEDs and molecular targets such as histone deacetylase and peroxisome proliferator-activated receptors may play a role in teratogenesis. Greater understanding of these factors may eventually permit an individualized assessment of teratogenic risk for WWE taking AEDs.[e5]

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DISCLOSURE

The authors report the following conflicts of interest: Dr. Harden has served on the scientific advisory board of Cyberonics, GlaxoSmithKline, UCB Pharma, Valeant, and SK Pharmaceuticals and on the speakers' bureau of GlaxoSmithKline, Pfizer, UCB Pharma, and Abbott. She serves as an editor of *Epilepsy Currents* and receives publishing royalties from Elsevier. Dr. Harden has received research funding from Forest, UCB Pharma, Ortho McNeil, and NIH/NINDS. Dr. Harden sees women with epilepsy in her office practice. Dr. Meador serves as a journal editor for *Neurology, Journal of Clinical Neurophysiology, Cognitive and Behavioral Neurology, Epilepsy & Behavior, Epilepsy Currents*, and Epilepsy.com. He has received research funding from NIH/NINDS, GlaxoSmithKline, Eisai, Marius, Myriad, Neuropace, SAM Technology, and UCB Pharma. Dr. Meador estimates that 30–40% of his clinical effort is spent on EEGs and the clinical care of patients with epilepsy. Dr. Pennell has served on the Expert Panel for the Keppra Pregnancy Registry sponsored by UCB Pharma. She has received funding for travel from the Northeast Regional Epilepsy Group for speaking at their 2008 Epilepsy Symposium, by the UK Research Council for speaking at the Epilepsy Research UK International Expert Workshop, by UCB Pharma for attending the Executive Panel meeting for the Pregnancy Registry, by the American Epilepsy Society for attending the Board of Directors' Meeting, by the Epilepsy Foundation for attending the Board of Directors' and orientation meetings, by the Long Island Jewish Hospital for lecturing at Neurology Grand Rounds, by Duke University for lecturing at Neurology Grand Rounds, by Brigham and Women's Hospital for lecturing at the Epilepsy Research Conference, by the Milken foundation for attending Pregnancy Registry meetings, and by Massachusetts General Hospital for speaking at the Annual Teratogens Course. She has received honoraria from Journal Watch Neurology for a contributing article, paid for by Massachusetts Medical Society, *NEJM*, for review for the *Lancet Neurology*, the Northeast Regional Epilepsy group for speaking at 2008 Epilepsy Symposium, North Shore Long Island Jewish Health system, Duke University, University of Maryland, the Massachusetts General Hospital for speaking at the postgraduate course in Human Teratogens, and the AAN for speaking and directing annual courses. Dr. Pennell has served as a contributing editor for *Epilepsy Currents* and is on the editorial board of *Epilepsia*. Dr. Pennell has received research support from UCB Pharma, Marinus Pharmaceuticals, NIH, NINDS, NIMH, CDC, and Emory University Research Council. Dr. Hauser has served on the scientific advisory board of Ovation and Valeant. He has served on the editorial board of *Acta Neurologica Scandinavia, Neuroepidemiology*, and *Epilepsy Research*. He has received honoraria from Cornell University Symposium on epilepsy and acted as a consultant to Pfizer. Dr. Hauser has received research support from AAMC/CDC, NIH/NINDS, FAA, Mayo Clinic, and Hotchkiss Neurological Institute, and has given expert testimony in his role as an FAA consultant. Dr. Gronseth serves as an editor of *Neurology Now* and on the speakers' bureau of Boehringer-Ingelheim. He receives compensation from the AAN for consulting work. Dr. French has served on the scientific advisory board of UCB Pharma, Johnson and Johnson, Eisai, Novartis, Valeant, Icagen, Intranasal, Sepracor, and Marinus. She has received funding for travel to present findings or give lectures from UCB Pharma, Kyowa, Eisai, Johnson and Johnson, Valeant, and GlaxoSmithKline. She has served as an associate editor for *Epilepsy Currents* and supplement editor for *Epileptic Disorders*. Dr. French is the president of the Epilepsy Study Consortium, which receives money from multiple pharmaceutical companies (including GlaxoSmithKline, UCB Pharma, Johnson and Johnson, Cyberonics, Schwarz Pharma, Ortho McNeil, Eisai, Jazz Pharmaceuticals, Ovation Pharmaceuticals, Endo Pharmaceuticals, Bial Pharmaceuticals, Neurovista, Valeant Pharmaceuticals, Icagen, Supernus, Intranasal, SK Pharmaceuticals, Taro Pharmaceuticals, Neurotherapeutics, Sepracor, and Novartis) and she consults on behalf of the consortium. Dr. French has received research funding from Johnson and Johnson, Eisai, UCB Pharma, SK Pharmaceuticals, Valeant, Pfizer, NIH, and Epilepsy Research Foundation. Dr. Wiebe serves on the editorial board of *Neurology, Epilepsia, Epilepsy & Behavior*, and *Canadian Journal of Neurological Sciences.* Dr. Thurman is an employee of the CDC. Dr. Koppel reports no disclosures. Dr. Kaplan has served on the speakers' bureau of UCB Pharma, GSK, and Ortho McNeil. He serves as an associate editor for *Neurophysiologie Clinique, Journal of Clinical Neurophysiology*, and *Epilepsia*. He receives royalties from Demos Publications for the books *Neurological Disease in Women, Epilepsy A to Z, Imitators of Epilepsy*, and *Nonconvulsive Status Epilepticus*. He has received speaker honoraria from Medical College of South Carolina, Duke University, and Medical College of Virginia, has received research funding from NIH, Schwarz, Ortho McNeil, and Pfizer, and has acted as a consultant for Schering-Plough and Infinite Biological Technologies. Dr. Robinson reports no disclosures. Dr. Hopp receives royalties from UpToDate.com electronic medical journal. She has been on the speakers' bureau of UCB Pharma and GlaxoSmithKline. Dr. Hopp has given testimony in a medico-legal case. Dr. Ting served on the scientific advisory board of UCB Pharma and has received honoraria from the Epilepsy Foundation of America. Dr. Gidal has served on the scientific advisory board for GlaxoSmithKline, UCB Pharma, and Abbott Labs and served as an editor for *Epilepsy & Behavior*, *The Annals of Pharmacotherapy*, and *Pharmacist's Letter.* Dr. Gidal has received research support from UCB Pharma. Dr. Hovinga estimates less than 10% of his clinical effort is spent on pharmacology consults. Dr. Wilner has served on the scientific advisory board of and received funding for travel from GlaxoSmithKline. He receives royalties from Demos Publications for *Epilepsy: 199 Answers* and *Epilepsy in Clinical Practice*. He receives board of directors compensation from GlaxoSmithKline. Dr. Vazquez has served on the scientific advisory board of Eisai, UCB, GSK, and Ortho McNeil. She has received honoraria from UCB, GSK, Ortho McNeil, and Eisai. Dr. Vazquez has served on a speakers' bureau for Eisai, GSK, Ortho McNeil, UCB, and Novartis. Dr. Holmes receives research support from Abbott Labs, Eisai, Novartis, Ortho McNeil, and Pfizer. Dr. Krumholz has served on the Department of Transportation Expert Panel on Commercial Drivers and Epilepsy and has served on the editorial board of *The Neurologist* and *Clinical EEG and Neuroscience*. He has received honoraria from the Robert Wood Johnson Medical School for grand

rounds. Dr. Finnell has served on the scientific advisory board of the NEAD study at Emory University, the University of Houston Center for Life Sciences Technology, the NIH, and the NIEHS National Advisory Environmental Health Sciences Council. He has received funding for travel from Fundacion BBVA, NIEHS National Advisory Environmental Health Sciences Council, IKMC Steering Committee, European Epilepsy Meeting, NIH, and AES. Dr. Finnell has served as a journal editor for *Birth Defects Research Part A* and holds a patent on folate receptor autoantibody assay. He has received honoraria from McGill University-Montreal Neurological Institute and has received research funding from the Centers for Disease Control and Prevention for the National Birth Defects Prevention Study and the Methodist Hospital Research Institute. Dr. Finnell has given expert testimony, prepared affadavits, and acted as a witness regarding legal proceedings related to the topic of this manuscript. Dr. Hirtz reports no disclosures. Ms. Le Guen reports no disclosures.

DISCLAIMER

This statement is provided as an educational service of the American Academy of Neurology. It is based on an assessment of current scientific and clinical information. It is not intended to include all possible proper methods of care for a particular neurologic problem or all legitimate criteria for choosing to use a specific procedure. Neither is it intended to exclude any reasonable alternative methodologies. The AAN recognizes that specific patient care decisions are the prerogative of the patient and the physician caring for the patient, based on all of the circumstances involved. The clinical context section is made available in order to place the evidence-based guideline(s) into perspective with current practice habits and challenges. No formal practice recommendations should be inferred. The findings and conclusions in the report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

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REFERENCES

1. United States Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Health Statistics, Bridged-Race Population Estimates, United States. July 1st resident population by state, county, age, sex, bridged-race, and Hispanic origin on CDC WONDER On-line Database. Available at: http://wonder.cdc.gov. Accessed June 2008.
2. Hirtz D, Thurman DJ, Gwinn-Hardy K, et al. How common are the "common" neurologic disorders? Neurology 2007;68:326–337.
3. Yerby MS. Quality of life, epilepsy advances, and the evolving role of anticonvulsants in women with epilepsy. Neurology 2000;55:S21–S31.
4. Harden CL, Hopp J, Ting TY, et al. Practice Parameter update: management issues for women with epilepsy—focus on pregnancy (an evidence-based review): obstetrical complications and change in seizure frequency: report of the Quality Standards Subcommittee and Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology and American Epilepsy Society. Neurology 2009;73:126–132.
5. Holmes LB, Harvey EA, Coull BA, et al. The teratogenicity of anticonvulsant drugs. N Engl J Med 2001;344:1132–1138.
6. Fried S, Kozer E, Nulman I, Einarson TR, Koren G. Malformation rates in children of women with untreated epilepsy. Drug Safety 2004;27:197–202.
7. Wide K, Winbladh B, Kallen B. Major malformations in infants exposed to antiepileptic drugs in utero, with emphasis on carbamazepine and valproic acid: a nation-wide, population-based register study. Acta Paediatr 2004;93:1774–1776.
8. Puho EH, Szunyogh M, Metneki J, Czeizel AE. Drug treatment during pregnancy and isolated orofacial clefts in Hungary. Cleft Palate Craniofac J 2007;4:194–202.
9. Arpino C, Brescianini S, Robert E, et al. Teratogenic effects of antiepileptic drugs: use of an international database on malformations and drug exposure (MADRE). Epilepsia 2000;41:1436–1443.
10. Morrow J, Russell A, Guthrie E, et al. Malformations risks of antiepileptic drugs in pregnancy: a prospective study from the UK Epilepsy and Pregnancy Register. J Neurol Neurosurg Psychiatry 2006;77:193–198.
11. Artama M, Auvinen A, Raudaskoski T, Isojarvi I, Isojarvi J. Antiepileptic drug use of women with epilepsy and congenital malformations in offspring. Neurology 2005;64:1874–1878.
12. Samrén EB, van Duijn CM, Christiaens GCML, Hofman A, Lindhout E. Antiepileptic drug regimens and major congenital abnormalities in the offspring. Ann Neurol 1999;46:739–746.
13. Vajda FJE, Hitchcock A, Graham J, et al. Foetal malformations and seizure control: 52 months data of the Australian Pregnancy Registry. Eur J Neurol 2006;13:645–654.
14. Meador KJ, Baker GA, Finnell RH, et al. In utero antiepileptic drug exposure: fetal death and malformations. Neurology 2006;67:407–412.
15. Canger R, Battino D, Canevini MP, et al. Malformations in offspring of women with epilepsy: a prospective study. Epilepsia 1999;40:1231–1236.
16. Wyszynski WF, Nambisan M, Surve T, Alsdorf RM, Smith CR, Holmes LB. Increased rate of major malformations in offspring exposed to valproate during pregnancy. Neurology 2005;64:961–965.
17. Agresti A. Categorical Data Analysis (Wiley Series in Probability and Statistics), 2nd edition. Malden, MA: Wiley-Interscience; 2002.
18. Mawer G, Clayton-Smith J, Coyle H, Kini U. Outcome of pregnancy in women attending an outpatient epilepsy clinic: adverse features associated with higher doses of sodium valproate. Seizure 2002;11:512–518.
19. Omtzigt JGC, Los FJ, Grobbee DE, et al. The risk of spina bifida aperta after first-trimester exposure to valproate in a prenatal cohort. Neurology 1992;42 (suppl 5):119–125.
20. Samrén EB, van Duijn CM, Koch S, et al. Maternal use of antiepileptic drugs and the risk of major congenital malformations: a joint European prospective study of human teratogenesis associated with maternal epilepsy. Epilepsia 1997;38:981–990.
21. Bertollini R, Mastoiacovo P, Segni G. Maternal epilepsy and birth defects: a case-control study in the Italian Multicenter Registry of Birth Defects (IPIMC). Eur J Epidemiol 1985;1:67–72.
22. Sattler JM. Assessment of Children revised/updated. 3rd ed. San Diego: Jerome M. Sattler; 1992.
23. Reinisch JM, Sanders SA, Mortensen EL, Rubin DB. In utero exposure to phenobarbital and intelligence deficits in adult men. JAMA 1995;274:1518–1525.
24. Gaily E, Kantola-Sorsa E, Hiilesmaa V, et al. Normal intelligence in children with prenatal exposure to carbamazepine. Neurology 2004;62:28–32.
25. Holmes LB, Rosenberger PB, Harvey EA, Khoshbin S, Ryan L. Intelligence and physical features of children of women with epilepsy. Teratology 2000;61:196–202.
26. Koch S, Titze K, Zimmermann RB, Schröder M, Lehmkuhl U, Rauh H. Long-term neuropsychological consequences of maternal epilepsy and anticonvulsant

treatment during pregnancy for school-age children and adolescents. Epilepsia 1999;40:1237–1243.
27. Oyen N, Vollset SE, Eide MG, Bjerkedal T, Skjærven R. Maternal epilepsy and offspring's adult intelligence: a population-based study from Norway. Epilepsia 2007;48:1731–1738.
28. Hirano T, Fujioka K, Okada M, Iwasa H, Kaneko S. Physical and psychomotor development in the offspring born to mothers with epilepsy. Epilepsia 2004;45(suppl 8):53–57.
29. Gaily E, Kantola-Sorsa E, Granström ML. Specific cognitive dysfunction in children with epileptic mothers. Dev Med Child Neurol 1990;32:403–414.
30. Wide K, Henning E, Tomson T, Winbladh B. Psychomotor development in preschool children exposed to antiepileptic drugs in utero. Acta Paediatr 2002;91:409–414.
31. Adab N, Kini U, Vinten J, et al. The longer term outcome of children born to mothers with epilepsy. J Neurol Neurosurg Psychiatry 2004;75:1575–1583.
32. Eriksson K, Viinikainen K, Mönkkönen A, et al. Children exposed to valproate in utero: population based evaluation of risks and confounding factors for long-term neurocognitive development. Epilepsy Res 2005;65:189–200.
33. Scolnik D, Nulman I, Rovet J, et al. Neurodevelopment of children exposed in utero to phenytoin and carbamazepine monotherapy. JAMA 1994;271:767–770.
34. Vanoverloop D, Schnell RR, Harvey EA, Holmes LB. The effects of prenatal exposure to phenytoin and other anticonvulsants on intellectual function at 4 to 8 years of age. Neurotoxicol Teratol 1992;14:329–335.
35. Lösche G, Steinhausen HC, Koch S, Helge H. The psychological development of children of epileptic parents: II: the differential impact of intrauterine exposure to anticonvulsant drugs and further influential factors. Acta Paediatr 1994;83:961–966.
36. Hvas CL, Henriksen TB, Ostergaard JR, Dam M. Epilepsy and pregnancy: effect of antiepileptic drugs and lifestyle on birth weight. Br J Obstet Gynaecol 2000;107:896–902.
37. Viinikainen K, Heinonen S, Eriksson K, Kalviainan R. Community-based, prospective, controlled study of obstetric and neonatal outcome of 179 pregnancies in women with epilepsy. Epilepsia 2006;47:186–192.
38. Hiilesmaa VK, Bardy A, Teramo K. Obstetric outcome in women with epilepsy. Am J Obstet Gynecol 1985;152:499–504.
39. Richmond JR, Krishnamoorthy P, Andermann E, Benjamin A. Epilepsy and pregnancy: an obstetric perspective. Am J Obstet Gynecol 2004;190:371–379.
40. Laskowska M, Leszczyriska-Gorzelak B, Oleszczuk J. Pregnancy in women with epilepsy. Gynecol Obstet Invest 2001;51:99–102.

The Child Neurology Society has endorsed the following guidelines:

- Management issues for women with epilepsy—Focus on pregnancy (an evidence-based review): Obstetrical complications and change in seizure frequency
- Management issues for women with epilepsy—Focus on pregnancy (an evidence-based review): Teratogenesis and perinatal outcomes
- Management issues for women with epilepsy—Focus on pregnancy (an evidence-based review): Vitamin K, folic acid, blood levels, and breastfeeding

Practice Parameter update: Management issues for women with epilepsy—Focus on pregnancy (an evidence-based review): Teratogenesis and perinatal outcomes: Report of the Quality Standards Subcommittee and Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology and American Epilepsy Society

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