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SPECIAL REPORT

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

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

***Cynthia L. Harden, †Kimford J. Meador, †Page B. Pennell, ‡W. Allen Hauser, §Gary S. Gronseth, ¶Jacqueline A. French, **Samuel Wiebe, ††David Thurman, ‡‡Barbara S. Koppel, §§Peter W. Kaplan, ¶¶Julian N. Robinson, ***Jennifer Hopp, ***Tricia Y. Ting, †††Barry Gidal, ‡‡‡Collin A. Hovinga, §§§Andrew N. Wilner, ¶¶¶Blanca Vazquez, ¶¶Lewis Holmes, ***Allan Krumholz, ****Richard Finnell, ††††Deborah Hirtz, and ‡‡‡‡Claire Le Guen**

***University of Miami, Miami, Florida, U.S.A.; †Emory University, Atlanta, Georgia, U.S.A.; ‡Columbia University, New York, U.S.A.; §Kansas University Medical Center, Kansas City, Kansas, U.S.A.; ¶New York University School of Medicine, New York, U.S.A.; **University of Calgary, Calgary, Alberta, Canada; ††Centers for Disease Control and Prevention, Atlanta, Georgia, U.S.A.; ‡‡New York Medical College, New York, U.S.A.; §§Johns Hopkins University, Baltimore, Maryland, U.S.A.; ¶¶Harvard Medical School, Boston, Massachusetts, U.S.A.; ***University of Maryland, Baltimore, Maryland, U.S.A.; †††University of Wisconsin–Madison School of Pharmacy; ‡‡‡University of Tennessee Health Science Center, Memphis, Tennessee, U.S.A.; §§§private practice, Newport, Rhode Island, U.S.A.; ¶¶¶New York University, New York, U.S.A.; ****Texas A&M University Health Science Center, Houston, Texas, U.S.A.; ††††National Institute of Neurological Disorders and Stroke, Bethesda, Maryland, U.S.A.; and ‡‡‡‡University of Pennsylvania, Philadelphia, Pennsylvania, U.S.A.**

Summary

A committee assembled by the American Academy of Neurology (AAN) reassessed the evidence related to the care of women with epilepsy (WWE) during pregnancy, including antiepileptic drug (AED) teratogenicity and adverse perinatal outcomes. It is highly probable that intrauterine first-trimester valproate (VPA) exposure has higher risk of major congenital malformations (MCMs) compared to carbamazepine (CBZ), and possibly compared to phenytoin (PHT) or lamotrigine (LTG). It is probable that VPA as part of polytherapy and possible that VPA as monotherapy contribute to the development of MCMs. AED polytherapy probably contributes to the development of MCMs and reduced cognitive outcomes compared to monotherapy. Intrauterine exposure to VPA monotherapy probably reduces cognitive outcomes and monotherapy exposure to PHT or phenobarbital (PB) 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. If possible, avoidance of VPA and AED polytherapy during the first trimester of pregnancy should be considered to decrease the risk of MCMs. If possible, avoidance of VPA and AED polytherapy throughout pregnancy should be considered and avoidance of PHT and PB throughout pregnancy may be considered to prevent reduced cognitive outcomes.

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Address correspondence to American Academy of Neurology, 1080 Montreal Avenue St. Paul, MN 55116, U.S.A. E-mail: guidelines@aan.com
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Recent estimates of the U.S. population (United States Department of Health and Human Services, 2007) and the prevalence of epilepsy (Hirtz et al., 2007) indicate approximately one-half million women with epilepsy (WWE) are of childbearing age and 3–5 births per thousand will be to WWE (Yerby, 2000). Epilepsy is defined by the presence of recurrent, unprovoked seizures, and 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 expect to participate in life experiences, including child-bearing.

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 birth weight, 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 (Harden et al., 2009).

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). Studies rated Class III or higher that contributed to conclusions are summarized in Tables e1–e5.

MCMs were defined as structural abnormalities with surgical, medical, or cosmetic importance (Holmes et al., 2001). 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 (Fried et al., 2004). 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 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 (Arpino et al., 2000; Wide et al., 2004; Puho et al., 2007) 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 (Morrow et al., 2006) 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 (Holmes et al., 2001) and OR 1.70, CI 1.07–2.68 (Artama et al., 2005)], found increased risks of MCMs with maternal AED exposure compared to untreated WWE.

Valproate

One Class II study (Artama et al., 2005) 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 (Morrow et al., 2006) 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 (Morrow et al., 2006) 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 (Morrow et al., 2006) 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 (Morrow et al., 2006) 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 (Morrow et al., 2006) and OR 2.51, CI 1.43–4.86) (Wide et al., 2004) revealed that VPA monotherapy is associated with a greater risk for MCMs than CBZ monotherapy.

One Class I study (Morrow et al., 2006) and one Class II study (Artama et al., 2005) showed that VPA as part of polytherapy was associated with greater risk than polytherapy without VPA (OR 2.49, CI 1.31–4.70 and OR 1.97, CI 0.58–6.66, respectively). One Class II study (Samrén et al., 1999) 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 (Canger et al., 1999; Meador et al., 2006; Vajda et al., 2006). All significant comparisons between AEDs are reported herein. In two Class III studies (Meador et al., 2006; Vajda et al., 2006), VPA was associated with increased risk when individually compared to CBZ [RR 4.34, CI 1.79–10.53 (Vajda et al., 2006) and RR 3.83, CI 1.41–10.39 (Meador et al., 2006] and LTG [RR 5.58, CI 2.06–15.09 (Vajda et al., 2006) and RR 17.04, CI 2.27–128.05 (Meador et al., 2006)]. The third Class III study (Canger et al., 1999) showed that VPA was associated with greater risk than phenobarbital (PB) (RR 5.66, CI 1.19–26.88).

All four Class III studies showed that 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 (Vajda et al., 2006) and RR 4.59, CI 2.07–10.18 (Meador et al., 2006)]. In the third Class III study, we compared VPA to PB, CBZ, PHT, and primidone (PRM) and found increased risk (RR 3.25, CI 1.27–8.33) (Canger et al., 1999). 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) (Wyszynski et al., 2005).

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 (Morrow et al., 2006) showed a moderately increased risk of MCMs with polytherapy versus monotherapy (RR 1.62, CI 1.14–2.31). Three Class II studies (OR 1.76, CI 0.94–3.31) (Artama et al., 2005), OR 2.00, CI 0.80–3.74 (Holmes et al., 2001), and OR 1.46, CI 0.83–2.56 (Samrén et al., 1999), 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 (Morrow et al., 2006), a relationship between AED dose and risk of MCMs was reported for LTG but not VPA. Using the Cochran Armitage method (Agresti, 2002), 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 (Samrén et al., 1999; Artama et al., 2005) and six Class III studies (Omtzigt et al., 1992; Samrén et al., 1997; Canger et al., 1999; Mawer et al., 2002; Meador et al., 2006; Vajda et al., 2006) 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 (Omtzigt et al., 1992; Samrén et al., 1997; Samrén et al., 1999; Mawer et al., 2002; Vajda et al., 2006).

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 (Morrow et al., 2006) showed increased risk of neural tube defects and facial clefts with VPA (RR 5.32, CI 1.38–20.50 and RR 4.18, CI 1.55–11.25, respectively). One Class II study (Puho et al., 2007) showed increased risk for cleft palate with PHT and posterior cleft palate with CBZ. Another Class II study (Samrén et al., 1999) showed increased risk of neural tube defects and hypospadias with VPA. Two Class III studies showed increased risk of spina bifida with VPA (Bertollini et al., 1985; Arpino et al., 2000), and one showed increased risk of hypospadias (Arpino et al., 2000). Two Class III studies (Arpino et al., 2000; Canger et al., 1999) 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 intelligence quotient (IQ) at age 2 years or older. Because maternal IQ has an important influence on child IQ (Sattler, 1992), 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 (Reinisch et al., 1995).

Is cognitive outcome reduced in children of WWE who are not exposed to AEDs in utero?

Two Class II studies (Holmes et al., 2000; Gaily et al., 2004) observed that cognition is not reduced in children of WWE unexposed to AEDs. One was a blinded observational study (Gaily et al., 2004) comparing the IQ of 64 children of WWE not taking AEDs with 121 controls. No important differences in IQ were found. The other study (Holmes et al., 2000) 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 (Koch et al., 1999; Oyen et al., 2007) and one Class III study (Hirano et al., 2004) showed reduced cognition in the children of WWE on AEDs. One Class II study (Gaily, 1990) and one Class III study (Wide et al., 2002) 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 (Adab et al., 2004; Gaily et al., 2004) and three Class III studies (Scolnik et al., 1994; Wide et al., 2002; Eriksson et al., 2005) showed CBZ does not increase the risk of poor cognitive outcomes compared to unexposed controls.

Valproate

Two Class II studies (Adab et al., 2004; Gaily et al., 2004) showed VPA poses an increased risk of poor cognitive outcomes compared to unexposed controls.

Phenytoin

One Class II study (Vanoverloop et al., 1992) and two Class III studies (Scolnik et al., 1994; Wide et al., 2002) 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 were found to have reduced cognitive abilities compared to normative populations (Reinisch et al., 1995).

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:

- Decreased cognitive outcome in the offspring of WWE should probably not be attributed to CBZ exposure (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 (Lösche et al., 1994; Koch et al., 1999; Gaily et al., 2004) 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 (Adab et al., 2004; Gaily et al., 2004) 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 PHT (Adab et al., 2004).

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 birth weight below the tenth 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 (Hvas et al., 2000; Viinikainen et al., 2006) 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) (Hvas et al., 2000). 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 (Viinikainen et al., 2006) 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. Furthermore, 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 studies (Hiilesmaa et al., 1985; Richmond et al., 2004) observed no increased risk of perinatal death (OR 0.57, CI 0.18–1.77) (Richmond et al., 2004). 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 (Viinikainen et al., 2006) 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%). Furthermore, this study showed increased rate of neonatal intensive care unit (ICU) 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 (Wilhelm et al., 1990; Laskowska et al., 2001) showed lowered Apgar scores compared to controls and three Class III studies (Hiilesmaa et al., 1985; Richmond et al., 2004; Pilo et al., 2006) 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. Furthermore, 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).

For other perinatal outcomes such as respiratory distress, intrauterine growth retardation, and neonatal ICU admission, there were not 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 (Chadwick, 2006).

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. Although VPA is an effective AED (Marson et al., 2007), it emerges as the AED with the greatest number of data showing an association with risk for 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 (Sankar, 2007).

Disclaimer

This statement is provided as an educational service of the American Academy of Neurology (AAN). 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 who is 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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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 and 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, HINDS, 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, 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 and 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 received 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 and Behaviour*, *Ann Pharmacotherapy*, and *Pharmacists 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 has received research funding from Abbott Labs, GlaxoSmithKline, 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.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Appendix e-1a. Mission statement of Quality Standards Subcommittee.

Appendix e-1b. Mission statement of Therapeutics and Technology Assessment Subcommittee.

Appendix e-2. Conflict of interest statement.

Appendix e-3a. Quality Standards Subcommittee (QSS) Members.

Appendix e-3b. Therapeutics and Technology Assessment Subcommittee Members.

Appendix e-4a. Classification of evidence for causality.

Appendix e-4b. Classification of evidence for rating of a prognostic article.

Appendix e-5a. Classification of recommendations.

Appendix e-5b. Classification of recommendations for causality.

Table e-1. MCMs in the children of treated WWE.

Table e-2. Risks of MCMs for specific AEDs as compared to others.

Table e-3. MCM risks of polytherapy versus monotherapy.

Table e-4. AED dosage in first trimester and MCMs.

Table e-5. AED-specific MCMs.

Table e-6. Teratogenesis of cognitive impairment in the offspring of WWE.

Table e-7. Adverse pregnancy outcomes.

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