Published in final edited form as:
Epilepsy Behav. 2009 July ; 15(3): 339–343. doi:10.1016/j.yebeh.2009.04.026.

Antiepileptic drug use in women of childbearing age

Kimford J. Meador[a,*], **Patricia Penovich**[b], **Gus A. Baker**[c], **Page B. Pennell**[a], **Edward Bromfield**[d], **Alison Pack**[e], **Joyce D. Liporace**[f], **Maria Sam**[g], **Laura A. Kalayjian**[h], **David J. Thurman**[i], **Eugene Moore**[a], and **David W. Loring**[a] **NEAD Study Group1**

[a] Neurology, Emory University, Atlanta, GA, USA

[b] Minnesota Epilepsy Group, St. Paul, MN, USA

[c] Walton Centre for Neurology & Neurosurgery, University of Liverpool, Merseyside, UK

[d] Neurology, Harvard–Brigham & Women's, Boston, MS, USA

[e] Neurology, Columbia University, New York City, NY, USA

[f] Riddle Health Care, Media, PA, USA

[g] Wake Forest University, Winston–Salem, NC, USA

[h] Neurology, University of Southern California, Los Angeles, CA, USA

[i] National Center for Chronic Disease Prevention and Health Promotion, Centers for Disease Control and Prevention, Atlanta, GA, USA

Abstract

Research on antiepileptic drug (AED) teratogenesis has demonstrated an increased risk for valproate. The impact of these findings on current AED prescribing patterns for women of childbearing age with epilepsy is uncertain. The Neurodevelopmental Effects of Antiepileptic Drugs (NEAD) Study is an ongoing prospective multicenter observational investigation that enrolled pregnant women with epilepsy on the most common AED monotherapies from October 1999 to February 2004 (carbamazepine, lamotrigine, valproate, and phenytoin). A 2007 survey of AED use in women of childbearing age at eight NEAD centers found a total of 932 women of childbearing age with epilepsy (6% taking no AED, 53% monotherapy, 41% polytherapy). The most common monotherapies were lamotrigine or levetiracetam. Since 2004, prescriptions of carbamazepine, phenytoin, and valproate have decreased, whereas those for levetiracetam have increased. Except for the top two AED monotherapies, there were marked differences in other monotherapies and in polytherapies between U.S. and UK centers. Future investigations are needed to examine reasons for drug choice.

* Corresponding author. Address: Department of Neurology, Emory University, Woodruff Memorial Research Building, 101 Woodruff Circle, Suite 6000, Mail Stop 1930-001-1AN, Atlanta, GA 30322, USA. Fax: +1 404 727 3157. kimford.meador@emory.edu (K.J. Meador).

[1]See Appendix for affiliations of the NEAD Study Group.

Conflict of interest statement: The authors have no disclosures.

Keywords

Antiepileptic drugs; Epilepsy; Women; Pregnancy; Teratogenesis; Drug choice; Prescription practices

1. Introduction

The first reports of antiepileptic drug (AED)-induced birth defects in humans date from the 1960s [1]. For many years, it has been known that the overall risk of major malformations across AEDs is increased about two- to threefold [2]. Higher dosages, higher blood levels, and polytherapy are associated with higher risks. In addition to anatomical teratogenesis, concerns have also been raised by animal and human studies that AEDs can produce behavioral teratogenesis, which results in cognitive impairment [3]. With the exception of an approximately 1.5% risk of neural tube defects with in utero valproate exposure [2], there has been little information available on differential AED risks until recently. The prior paucity of information on differential AED risks is reflected in the last published consensus guidelines of the American Academy of Neurology [4], American College of Obstetricians and Gynecologists [5], and International League Against Epilepsy [6]. None of these guidelines delineated differential teratogenetic risks across AEDs.

In recent years, there has been a marked increase in information concerning AED teratogenesis based in large part on the formation of multiple pregnancy registries. A consistent finding has emerged indicating that valproate poses an increased risk to the unborn child [7–19]. This differential risk includes both anatomical and behavioral teratogenetic defects, both of which are dose dependent. Six of the studies implicating an increased risk for valproate were published in 2004, with an additional three in 2005. A recent meta-analysis examining AED anatomical teratogenesis indicated that in utero valproate exposure is associated with a 10.73% (95% CI: 8.16–13.29) risk of major malformations, which occurred across multiple body systems [20]. In utero valproate exposure has also been associated with reduced cognitive abilities in four patient cohorts [8–10,19]. This suggests that the risk of valproate extends throughout pregnancy, as the risk of anatomical defects is due to first-trimester exposure [2], and the risk for behavioral defects appears to be due primarily to third-trimester exposure [3].

Data for other AEDs are less clear or even completely lacking. Based on fewer studies, there appears to be an increased risk of anatomical and behavioral defects with phenobarbital [21, 22]. Overall risks for carbamazepine and lamotrigine exposure are low [16–18,23], but a risk for cleft lip/palate has been reported for both. According to one study [24] and preliminary [25] results from another, the risk of cleft lip/palate is increased with carbamazepine. In one report on lamotrigine, an increased risk of cleft lip/palate was observed [23], but another study found contradictory results for lamotrigine [26]. In addition, one registry has described a dose-dependent effect for lamotrigine [16], but this was not confirmed by two other studies [23, 27]. Preliminary studies with levetiracetam suggest low risk, but small sample sizes limit conclusions [28]. Small sizes and mixed results limit conclusions about topiramate [29,30]. In utero phenytoin exposure has been reported to impair cognitive functions in three studies [31–33] that did not control for maternal IQ, but phenytoin was not statistically worse than carbamazepine or lamotrigine according to the results of a prospective study [19] that did control for maternal IQ. Because the most compelling findings for human teratogenesis are those found consistently across different studies, the risks for AEDs other than valproate remain uncertain.

Published information is lacking on current AED prescribing patterns for women of childbearing age with epilepsy. The purpose of the present study was to examine changes in

prescription practices at tertiary epilepsy centers as a result of the demonstrated increased risks for valproate and the emerging information on teratogenetic risks of other AEDs.

2. Methods

Both the original Neurodevelopmental Effects of Antiepileptic Drugs (NEAD) study and the 2007 survey were approved by the institutional review board at each participating center and were conducted in accordance with the ethical standards delineated in the 1964 Declaration of Helsinki. The NEAD Study is a prospective observational National Institutes of Health (NIH)-funded investigation, and enrolled 333 mother/child pairs during pregnancy from October 1999 to February 2004 across 26 epilepsy centers in the United States and United Kingdom [16]. The primary aim of the NEAD Study was to determine differential long-term neurodevelopmental effects of in utero AED exposure. The study focused on the four most commonly used AED monotherapies (i.e., carbamazepine, lamotrigine, phenytoin, or valproate) during that period, because these four AEDs were by far the most commonly used AEDs at these centers. The number of women on other AED monotherapies was too small to generate adequate samples.

The 2007 survey of prescription practices for women of childbearing age, including the subset who were pregnant, involved a subset of NEAD centers ($n = 8$) participating in the original investigation. The centers in the 2007 survey enrolled 54% of the original sample. The centers in the 2007 survey study included: Minnesota Epilepsy Group, University of Liverpool, Emory University, Harvard–Brigham & Women's, Columbia University, Riddle Health Care, Wake Forrest University, and University of Southern California. Additional centers in the NEAD Study included: Arizona Health Sciences Center, Baylor Medical Center, Case Western Reserve University, Georgetown University, Harvard–Massachusetts General, Henry Ford Hospital, Medical College of Cornell University, Medical College of Georgia, Ohio State University, Rush University Medical Center, The Comprehensive Epilepsy Care Center for Children and Adults (St. Louis, MO, USA), St. Mary's Hospital (Manchester, UK), University of Alabama—Birmingham, University of Cincinnati, University of Kansas School of Medicine—Wichita, University of Miami, University of Texas—Southwestern, University of Washington, and University of Utah. The survey was conducted from June into November 2007. Institutional review boards at each clinical center approved the NEAD Study and the present survey study.

2.1. Participants

The 2007 survey included women with epilepsy, between the ages of 12 and 45, who were pregnant or who were of childbearing age. The NEAD Study included pregnant women on one of the four aforementioned AED monotherapies.

2.2. Procedure

Surveys were filled out by local investigators who obtained the information from the clinical records of patients presenting to their epilepsy clinics who met the above eligibility criteria during the study period. The diagnosis of epilepsy was confirmed, and the following information was obtained from the medical records: age, pregnancy status, and number/types of current AED treatments.

2.3. Statistical analyses

Descriptive summary statistical information was calculated. X^2 contingency analyses were conducted comparing distributions of: (1) treatment (i.e., no AED, monotherapy, polytherapy) for pregnant versus nonpregnant women, (2) types of AED monotherapy for pregnant versus nonpregnant women, (3) monotherapy for the four AEDs in the NEAD Study (across the eight

centers in the present survey) compared with the same four drugs in pregnant women from the 2007 survey, and (4) types of AED monotherapy for the United States versus the United Kingdom.

3. Results

There were a total of 932 women in the 2007 survey; 793 were from the United States, and 139 were from the United Kingdom. The mean age of the women was 30 years (±8.7). Pregnant women constituted 11% of the sample. See Table 1 for the survey distribution of monotherapy, polytherapy, and no AED exposure, which differed between pregnant and nonpregnant women ($X^2 = 37.0$, $P \leq 0.000$). Pregnant women were more likely to be on no AED or monotherapy, but less likely to be on polytherapy than nonpregnant women. AED monotherapy did not differ significantly between pregnant and nonpregnant women ($X^2 = 14.2$, $P = 0.076$). Monotherapies employed differed between the United States and United Kingdom ($X^2 = 28.0$, $P \leq 0.000$) (see Supplementary Table 1). Lamotrigine was the most commonly used AED in both countries, but levetiracetam, oxcarbazepine, topiramate, and zonisamide were used more often in the United States, whereas carbamazepine and valproate were used more often in the United Kingdom.

The four AEDs used in monotherapy in the NEAD Study (1999–2004) changed in the eight centers by the 2007 survey ($X^2 = 22.0$, $P \leq 0.0001$) (see Table 2). There was a relative increase in lamotrigine use and a relative decrease in the use of carbamazepine, phenytoin, and valproate in 2007 compared with the earlier period. Across the entire 2007 survey, the top four AEDs in order of decreasing use were lamotrigine, levetiracetam, carbamazepine and topiramate compared to carbamazepine, lamotrigine, phenytoin, and valproate during NEAD enrollment.

Polytherapy was used in 41% of the survey sample overall. Of those on polytherapy, 65% were on two AEDs, 28% on three AEDs, and 7% on four or more AEDs. Polytherapy choices varied widely (see Supplementary Table 2). The most common two-AED combination in the United States (i.e., lamotrigine–levetiracetam) constituted 20% of two AED polytherapies in the United States, but only 3% in the United Kingdom. The most common two-AED polytherapy in the United Kingdom (i.e., carbamazepine–levetiracetam) constituted 18% of two-AED polytherapies in the United Kingdom, but only 5% in the United States. Further, 44% of two-AED polytherapies comprised less than 4% of the two-AED polytherapies on an individual basis.

4. Discussion

This report describes changes over the past several years in AED prescription practices in women with epilepsy at epilepsy specialty centers in the United States and United Kingdom. During the original recruitment period for the NEAD Study (October 1999 to February 2004), the four most commonly used AEDs in descending order in pregnant women with epilepsy at epilepsy specialty centers were carbamazepine, lamotrigine, valproate, and phenytoin [16, 19]. By 2007, the four most commonly used AEDs in women of childbearing age with epilepsy in the specialty centers were lamotrigine, levetiracetam, carbamazepine, and topiramate.

Given that multiple publications have described an association with in utero valproate exposure, it is not surprising that valproate use declined in women being treated at epilepsy specialty centers. Less clear from an evidence-based medical approach is the apparent decline in carbamazepine use despite its relatively mild adverse teratogenesis profile, which is similar to that of lamotrigine. Carbamazepine was actually used by the largest number of patients in pregnancy-related studies prior to 2007. The causes of the reduced usage of carbamazepine are unclear, but may include tolerability (e.g., cognitive and other side effects), drug interactions,

or marketing factors. Phenytoin use has decreased by an even larger proportion at epilepsy specialty centers. The increase in levetiracetam use may be based on several factors including: the promising but very limited preliminary human birth defect data published by the UK Registry in 2006 [28] and general tolerability, safety, efficacy, and lack of neuronal apoptosis in animal studies [34,35]. However, it should be reemphasized that the present teratogenic data for levetiracetam, like those for many AEDs, are inadequate to be certain.

Compared with nonpregnant women of childbearing age, pregnant women were more likely to be on AED monotherapy than polytherapy. Although this may be an attempt to avoid the risks of polytherapy during pregnancy, it may also reflect increased difficulty in conception in women on polytherapy because of the AEDs or the increased severity of epilepsy.

Although lamotrigine was the most common AED monotherapy in the United States and United Kingdom, other monotherapies differed across the two countries. Even greater variability was seen in the choice of polytherapies. For example, examination of the two-AED polytherapy combinations in the survey reveals that the top nine AED combinations ranged from 4 to 18% individually of all two-AED combinations, and that the remaining combinations, which were all less than 4% each individually, constituted 44% of all two-AED polytherapy combinations. This variability likely reflects a lack of evidence-based medical data to inform and direct therapy.

Strengths of our study include repeated assessments of AED use in a set of epilepsy specialty centers. Our study has several limitations. Only 8 of the original 25 epilepsy specialty centers were included in the 2007 survey, but these 8 centers enrolled 54% of the original subjects, and the distribution of AEDs in 1999–2004 in these centers was similar to the entire sample. In 2007, we assessed primarily use of AEDs in women with epilepsy of childbearing age and not specifically women with epilepsy of childbearing potential. Thus, AED selection might differ in those of childbearing age who do not have childbearing potential. Another limitation is that our study does not specifically address the reasons for the changes (or absence of changes) seen over this period.

The reported data provide a window into current AED use in women, but the findings may not apply to all epilepsy specialty centers, much less the entire general medical population. Although data from 2007 are not yet available, a general medical population estimate is available from public-use data for the years 2000–2006 from the National Center for Health Statistics [36], which includes the National Ambulatory Medical Care Survey (NAMCS) and the National Hospital Ambulatory Medical Care Survey (NHAMCS). These data reveal that the two most commonly used AEDs for epilepsy or seizures in women of childbearing age were phenytoin and valproate across the entire period 2000–2006. The data from the general medical population and the NEAD centers are not directly comparable because they differ in last year of assessment (2006 vs 2007), and there is a lack of information on the patient populations (e.g., pregnancy, co-morbidities, refractoriness). Despite these limitations, data from the general medical population differ markedly from data from the tertiary centers at the beginning of the century and suggest that the new information on teratogenetic risks for valproate has had little effect on the prescription practices for women of childbearing age in the general medical population through 2006.

Factors that may affect drug choice include efficacy, approved indications, side effects (including AED teratogenesis), drug interactions, past medical history, present comorbidities, costs, and marketing. The interaction of multiple factors, which are at times conflicting, can make drug choice difficult for an individual patient. Further complicating drug choice is an inadequate database for many factors. For example, direct head-to-head comparisons of efficacy and side effects are not available for most AEDs. In the absence of adequate evidence-

based data, rational therapeutic practice is a challenge. Nevertheless, the factors driving changes in AED prescriptions to women of childbearing age are not completely clear.

The recent increase in information concerning AED teratogenesis improves our ability to care for women of childbearing potential, but it also complicates therapeutic decisions. Previous guidelines have simply recommended that physicians choose the most effective AED for the individual woman. Now physicians must consider factors related to teratogenetic risks for specific AEDs, although the evidence for some risks and many AEDs remains uncertain. Even the definite increased risk of valproate has to be balanced against considerations of efficacy [37]. Neither teratogenesis nor efficacy for seizure control can be predicted on an individual patient basis. We have previously recommended that valproate not be used as a first-line AED in women of childbearing potential, because the failure to control seizures may be corrected by altering the AED, but the occurrence of teratogenesis is frequently irreversible and results in lifelong disability [17]. If valproate is used in a woman of childbearing potential, the lowest effective dose should be employed, as valproate's teratogenic risk is dose dependent. The informed consent process must include a discussion of these various factors as they relate to the individual woman. The discussion should occur when the AED is first prescribed and should provide advice concerning the certainty of the information available so that the patient can participate fully in the decision process.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This study was supported by Grants 2 RO1 NS038455 from the NIH/NINDS, 1 R01050659 from the NIH/NINDS, and RB219738 from the UK Epilepsy Research Foundation. The investigators thank the children and families who have given their time to participate in the NEAD Study. The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the Centers for Disease Control and Prevention.

Role of the funding source: The NINDS DSMB has reviewed and made recommendations for the design, data collection, and analyses of the parent NEAD Study; they have also reviewed this substudy and article.

Appendix

Appendix A. NEAD Study Group

Arizona Health Sciences Center, Tucson, AZ, USA: David Labiner, M.D., Jennifer Moon, Ph.D., Scott Sherman, M.D.; Baylor Medical Center, Irving TX, USA: Deborah T. Combs Cantrell, M.D., University of Texas—Southwestern, Dallas TX, USA: Cheryl Silver, Ph.D.; Case Western Reserve University, Cleveland, OH, USA: Monisha Goyal, M.D., Mike R. Schoenberg, Ph.D.; Columbia University, New York City, NY, USA: Alison Pack, M.D., Christina Palmese, Ph.D, Joyce Echo, Ph.D; Emory University, Atlanta, GA, USA: Page Pennell, M.D., Megan Denham, M.A.Ed., Charles Epstein, M.D., Jennifer Gess, Ph.D., Sandra Helmers, M.D., Thomas Henry, M.D.; Georgetown University, Washington, DC, USA: Gholam Motamedi, M.D., Erin Flax, BS; Harvard–Brigham & Women's, Boston, MA, USA: Edward Bromfield, M.D., Katrina Boyer, Ph.D., Barbara Dworetzky, Sc.B., M.D.; Harvard–Massachusetts General, Boston, MA: Andrew Cole, M.D., Lucila Halperin, B.A., Sara Shavel-Jessop, B.A.; Henry Ford Hospital, Detroit, MI: Gregory Barkley, M.D., Barbara Moir, M.S.; Medical College of Cornell University, New York City, NY, USA: Cynthia Harden, M.D., Tara Tamny-Young, Ph.D.; Medical College of Georgia, Augusta, GA, USA: Gregory Lee, Ph.D., Morris Cohen, Ed.D.; Minnesota Epilepsy Group, St. Paul, MN, USA: Patricia Penovich, M.D., Donna Minter, Ed.D.; Ohio State University, Columbus, OH, USA: Layne Moore, M.D., Kathryn Murdock, M.A.; Riddle Health Care, Media, PA, USA: Joyce Liporace,

M.D., Kathryn Wilcox, B.S.; Rush University Medical Center, Chicago, IL, USA: Andres Kanner, M.D., Michael N. Nelson, Ph.D.; The Comprehensive Epilepsy Care Center for Children and Adults, St. Louis, MO, USA: William Rosenfeld, M.D., Michelle Meyer, M.Ed.; St. Mary's Hospital, Manchester, UK: Jill Clayton-Smith, M.D., George Mawer, M.D., Usha Kini, M.D.; University of Alabama, Birmingham, AL, USA: Roy Martin, Ph.D.; University of Cincinnati, Cincinnati, OH, USA: Michael Privitera, M.D., Jennifer Bellman Psy.D., David Ficker, M.D.; University of Florida, Gainesville, FL, USA: Kimford J. Meador, M.D., David Loring, Ph.D., Eugene Moore, B.S.; University of Kansas School of Medicine—Wichita, Wichita, KS, USA: Lyle Baade, Ph.D., Kore Liow, M.D.; University of Liverpool, Liverpool, UK: David Chadwick, M.D., Gus Baker, Ph.D., Alison Booth, BSc, Rebecca Bromley, B.Sc., Sara Dutton, B.Sc., James Kelly, B.Sc., Jenna Mallows, B.Sc., Lauren McEwan, M.Sc., Laura Purdy, B.Sc.; University of Miami, Miami, Florida: Eugene Ramsay M.D., Patricia Arena Ph.D.; University of Southern California, Los Angeles, CA, USA: Laura Kalayjian, M.D., Christianne Heck, M.D., Sonia Padilla, PsyD; University of Washington, Seattle, WA, USA: Daniel Drane, Ph.D., John Miller, M.D., Gail Rosenbaum, B.A., Alan Wilensky, M.D.; University of Utah, Salt Lake City, UT, USA: Tawnya Constantino, M.D., Julien Smith, Ph.D.; Walton Centre for Neurology & Neurosurgery, Liverpool, UK: Naghme Adab, M.D., Gisela Veling-Warnke, M.D.; Wake Forest University, Winston-Salem, NC, USA: Maria Sam, M.D., Cormac O'Donovan, M.D., Cecile Naylor, Ph.D., Shelli Nobles, M.S., Cesar Santos, M.D., William Bell, M.D.

A.1. Executive Committee

Dartmouth Medical School, Hanover, NH, USA: Gregory Holmes, M.D.; Stanford University, Stanford, CA, USA: Maurice Druzin, M.D., Martha Morrell, M.D., Lorene Nelson, Ph.D.; Texas A&M University Health Science Center, Houston, TX, USA: Richard Finnell, Ph.D.; University of Oregon, Portland, OR, USA: Mark Yerby, M.D.; University of Toronto, Toronto, ON, Canada: Khosrow Adeli Ph.D., Peter Wells, Pharm.D.

A.2. Data and statistical center

EMMES Corporation, Rockville, MD, USA: Temperance Blalock, A.A., Nancy Browning, Ph.D., Linda Hendrickson, Bernadette Jolles, M.A., Michelle LaMotteo, B.S., Cristina Murray-Krezan, M.S., Steve Russell, B.S., Charles Servis, B.S., Jamie Winestone, B.S., Mark Wolff, Ph.D., Phyllis Zaia, B.S., Thad Zajdowicz, M.D., MPH, FACP.

Appendix B. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi: 10.1016/j.yebeh.2009.04.026.

References

1. Mullers-Kuppers VM. Embryopathy during pregnancy caused by taking anticonvulsants. Acta Paedopsychiatr 1963;30:401–5. [PubMed: 14093746]
2. Finnell, RH.; Nau, H.; Yerby, MS. General principles: teratogenicity of antiepileptic drugs. In: Levy, RH.; Mattson, RH.; Meldrum, BS., editors. Antiepileptic drugs. New York: Raven Press; 1995. p. 209-30.
3. Gaily, E.; Meador, KJ. Neurodevelopmental effects. In: Engel, J.; Pedley, TA., editors. Epilepsy: a comprehensive textbook. Vol. 2nd. Vol. II. Philadelphia: Lippincott Williams & Wilkins; 2007. p. 1225-33.
4. Practice parameter: management issues for women with epilepsy [summary statement]. Report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology 1998;51:944–8. [PubMed: 9781510]

5. Committee on Educational Bulletins of the American College of Obstetricians and Gynecologists. ACOG educational bulletin: seizure disorders in pregnancy. Int J Gynaecol Obstet 1997;56:279–86. [PubMed: 9127164]
6. Commission on Genetics, Pregnancy and the Child, International League Against Epilepsy. Guidelines for the care of women of childbearing age with epilepsy. Epilepsia 1993;43:588–9.
7. Samren EB, van Duijn CM, Christiaens GCML, Hofman A, Lindhout E. Antiepileptic drug regimens and major congenital abnormalities in the offspring. Ann Neurol 1999;46:739–46. [PubMed: 10553991]
8. Adab N, Jacoby A, Smith D, Chadwick D. Additional educational needs in children born to mothers with epilepsy. J Neurol Neurosurg Psychiatry 2001;70:15–21. [PubMed: 11118242]
9. Adab N, Kini U, Vinten J, et al. The longer term outcome of children born to mothers with epilepsy. J Neurol Neurosurg Psychiatry 2004;75:1575–83. [PubMed: 15491979]
10. Gaily E, Kantola-Sorsa E, Hiilesmaa V, et al. Normal intelligence in children with prenatal exposure to carbamazepine. Neurology 2004;62:28–32. [PubMed: 14718692]
11. Vajda FJ, O'Brien TJ, Hitchcock A, et al. Critical relationship between sodium valproate dose and human teratogenicity: results of the Australian register of anti-epileptic drugs in pregnancy. J Clin Neurosci 2004;11:854–8. [PubMed: 15519862]
12. Wide K, Winbladh B, Källén 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;93:174–6. [PubMed: 15046269]
13. Artama M, Auvinen A, Raudaskoski T, Isojärvi I, Isojärvi J. Antiepileptic drug use of women with epilepsy and congenital malformations in offspring. Neurology 2005;64:1874–8. [PubMed: 15955936]
14. Cunnington M, Tennis P. International Lamotrigine Pregnancy Registry Scientific Advisory Committee. Lamotrigine and the risk of malformations in pregnancy. Neurology 2005;64:955–60. [PubMed: 15781807]
15. Wyszynski DF, Nambisan M, Surve T, Alsdorf RM, Smith CR, Holmes LB. Antiepileptic Drug Pregnancy Registry. Increased rate of major malformations in offspring exposed to valproate during pregnancy. Neurology 2005;64:961–5. [PubMed: 15781808]
16. Morrow JI, Russell A, Gutherie E, et al. Malformation risks of anti-epileptic drugs in pregnancy: a prospective study from the UK Epilepsy and Pregnancy Register. J Neurol Neurosurg Psychiatry 2006;77:193–8. [PubMed: 16157661]
17. Meador KJ, Baker GA, Finnell RH, et al. NEAD Study Group. In utero antiepileptic drug exposure: fetal death and malformations. Neurology 2006;67:407–12. [PubMed: 16894099]
18. 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;13:645–54. [PubMed: 16796590]
19. Meador KJ, Baker GA, Browning N, et al. NEAD Study Group. Fetal antiepileptic drug exposure and cognitive function at age 3. N Engl J Med 2009;360:1597–605. [PubMed: 19369666]
20. Meador KJ, Reynolds MW, Crean S, Fahrbach K, Probst C. Pregnancy outcomes in women with epilepsy: a systematic review and meta-analysis of published pregnancy registries and cohorts. Epilepsy Res 2008;81:1–13. [PubMed: 18565732]
21. Holmes LB, Wyszynski DF, Lieberman E. The AED (antiepileptic drug) pregnancy registry: a 6-year experience. Arch Neurol 2004;61:673–8. [PubMed: 15148143]
22. Reinisch JM, Sanders SA, Mortensen EL, et al. In utero exposure to phenobarbital and intelligence deficits in adult men. JAMA 1995;274:1518–25. [PubMed: 7474220]
23. Holmes LB, Baldwin EJ, Smith CR, et al. Increased frequency of isolated cleft palate in infants exposed to lamotrigine during pregnancy. Neurology 2008;70:2152–8. [PubMed: 18448870]
24. Puho EH, Szunyogh M, Metneki J, Czeizel AE. Drug treatment during pregnancy and isolated orofacial clefts in Hungary. Cleft Palate-Craniofacial J 2007;4:194–202.
25. Hernandez-Diaz S, Smith CR, Wyszynski DF, Holmes LB. Risk of major malformations among infants exposed to carbamazepine during pregnancy. Birth Defects Res 2007;79:357.abstract
26. Dolk H, Jentink J, Loane M, Morris J, De Jong-van den Berg LTW, EUROCAT Antiepileptic Drug Working Group. Does lamotrigine use in pregnancy increase orofacial cleft risk relative to other malformations? Neurology 2008;71:714–22. [PubMed: 18650491]

27. Cunnington M, Ferber S, Quartey G. International Lamotrigine Pregnancy Registry Scientific Advisory Committee. Effect of dose on the frequency of major birth defects following fetal exposure to lamotrigine monotherapy in an international observational study. Epilepsia 2007;48:1207–10. [PubMed: 17381445]

28. Hunt S, Craig J, Russell A, et al. Levetiracetam in pregnancy: preliminary experience from the UK Epilepsy and Pregnancy Register. Neurology 2006;67:1876–9. [PubMed: 17130430]

29. Ornoy A, Zvi N, Arnon J, Wajnberg R, Shechtman S, Diav-Citrin O. The outcome of pregnancy following topiramate treatment: a study on 52 pregnancies. Reprod Toxicol 2008;25:388–9. [PubMed: 18424066]

30. Hunt S, Russell A, Smithson WH, et al. UK Epilepsy and Pregnancy Register. Topiramate in pregnancy: preliminary experience from the UK Epilepsy and Pregnancy Register. Neurology 2008;71:272–6. [PubMed: 18645165]

31. 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;14:329–35. [PubMed: 1454041]

32. Scolnik D, Nulman I, Rovet J, et al. Neurodevelopment of children exposed *in utero* to phenytoin and carbamazepine monotherapy. JAMA 1994;271:767–70. [PubMed: 7509419]

33. Wide K, Henning E, Tomson T, Winbladh B. Psychomotor development in preschool children exposed to antiepileptic drugs *in utero*. Acta Paediatr 2002;91:409–14. [PubMed: 12061356]

34. Manthey D, Asimiadou S, Stefovska V, et al. Sulthiame but not levetiracetam exerts neurotoxic effect in the developing rat brain. Exp Neurol 2005;193:497–503. [PubMed: 15869952]

35. Kim J, Kondratyev A, Gale K. Antiepileptic drug-induced neuronal cell death in the immature brain: effects of carbamazepine, topiramate, and levetiracetam as monotherapy versus polytherapy. J Pharmacol Exp Ther 2007;323:165–73. [PubMed: 17636003]

36. Centers for Disease Control and Prevention, National Center for Health Statistics. Ambulatory health care data. 2008 [accessed 17.09.08]. <http://www.cdc.gov/nchs/about/major/ahcd/ahcd1.htm>

37. Marson AG, Al-Kharusi AM, Alwaidh M, et al. The SANAD study of effectiveness of valproate, lamotrigine, or topiramate for generalised and unclassifiable epilepsy: an unblinded randomised controlled trial. Lancet 2007;369:1016–26. [PubMed: 17382828]

Table 1

Antiepileptic drugs in women of childbearing age with epilepsy in 2007.

	Overall	Nonpregnant	Pregnant
N	932	833	99
No AED	52 (6%)	42 (5%)	10 (10%)
Monotherapy	495 (53%)	419 (50%)	76 (77%)
Polytherapy	385 (41%)	372 (45%)	13 (13%)

Table 2

Monotherapy antiepileptic drugs in women of childbearing age.

	Overall 2007 survey	2007 survey restricted to 4 AEDs	NEAD Study for 8 centers in survey[a]	NEAD Study overall
N	495	307	207	333
Lamotrigine	180 (36%)	180 (57%)	70 (34%)	98 (29%)
Levetiracetam	87 (18%)	–	–	–
Carbamazepine	70 (14%)	70 (23%)	61 (29%)	110 (33%)
Topiramate	47 (9%)	–	–	–
Valproate	40 (8%)	40 (13%)	37 (18%)	69 (21%)
Zonisamide	20 (4%)	–	–	–
Phenytoin	17 (3%)	17 (6%)	39 (19%)	56 (17%)
Oxcarbazepine	11 (2%)	–	–	–
Other	23 (5%)	–	–	–

[a] Includes women enrolled in the NEAD Study for the eight centers participating in the subsequent survey. Note that these four AEDs were by far the most often used by pregnant women during the NEAD enrollment period (October 1999–February 2004).