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BRIEF COMMUNICATION

Utilization of antiepileptic drugs during pregnancy: Comparative patterns in 38 countries based on data from the EURAP registry

The EURAP Study Group[1]

Summary

We assessed the utilization of antiepileptic drugs (AEDs), 1999–2005, in 4,798 prospective epilepsy pregnancies from 38 countries participating in EURAP, an international AED and pregnancy registry. Prominent differences in utilization patterns were observed across the various countries. Exposure to second-generation AEDs ranged from 3.5% in India and 7.3% in Italy to 75% in Denmark. Even wider variation was recorded in exposure to individual AEDs. The utilization of second-generation AEDs increased over time (for lamotrigine, from 9.9% of all pregnancies before 2001 to 29.6% after 2003). The differences in use of individual AEDs across countries probably reflect lack of evidence concerning the optimal treatment of epilepsy in women of childbearing age, as well as variation in country-specific traditions, medication costs, and drug promotion. Our observations underscore the need for comparative studies to investigate the factors influencing the prescription of AEDs during pregnancy, as well as their influence on pregnancy outcome.

KEY WORDS: Epilepsy, Pregnancy, Antiepileptic drugs, Drug utilization.

With insufficient data to support an evidence-based approach to the management of epilepsy in women of childbearing potential (Commission on Genetics, Pregnancy, and the Child International League Against Epilepsy, 1993; Tomson et al., 2004), treatment strategies in these women are likely to be influenced by other factors such as local traditions, cost and availability of drugs, and drug promotion, all of which vary across geographic regions. EURAP is an international pregnancy registry that aims primarily at assessing the teratogenic potential of individual antiepileptic drugs (AEDs) and their combinations (EURAP Study Group, 2006). Women treated with AEDs at the time of conception are enrolled early in pregnancy, and details on their treatment are recorded. We used the EURAP database to analyze AED utilization during pregnancy in 4,798 prospective pregnancies from 38 countries, assessing prescription patterns by country and their changes over a 5-year period: 1999–2005.

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[1]The complete list of collaborators is given in Appendix 1.

Patients and Methods

EURAP methodology has been described elsewhere (EURAP Study Group, 2006). Women are enrolled in early pregnancy by a network of physicians. Enrollment started in Italy, Australia, and Sweden in 1999. At the end of December 2005, 4,798 pregnancies in 4,100 women with epilepsy from 38 countries had been enrolled and followed prospectively. Enrollment by country is summarized in Fig. 1.

Exposures to specific AED regimens at enrollment (monotherapy vs. polytherapy, first- vs. second-generation AEDs, and individual AEDs in monotherapy) were compared across countries. When appropriate, rates and means with 95% confidence intervals (CIs) were calculated.

Exposures to individual AEDs accounting for <2% of the cases were pooled as "other monotherapies with first generation AEDs" (barbexaclone, primidone, clobazam, ethosuximide, acetazolamide, and sulthiame) or "other monotherapies with second-generation AEDs" (topiramate, levetiracetam, gabapentin, vigabatrin, felbamate, and zonisamide). AEDs analyzed individually included carbamazepine (CBZ), valproate (VPA), phenobarbital (PB), and phenytoin (PHT) among first-generation drugs, and lamotrigine (LTG) and oxcarbazepine (OXC) among second-generation drugs.

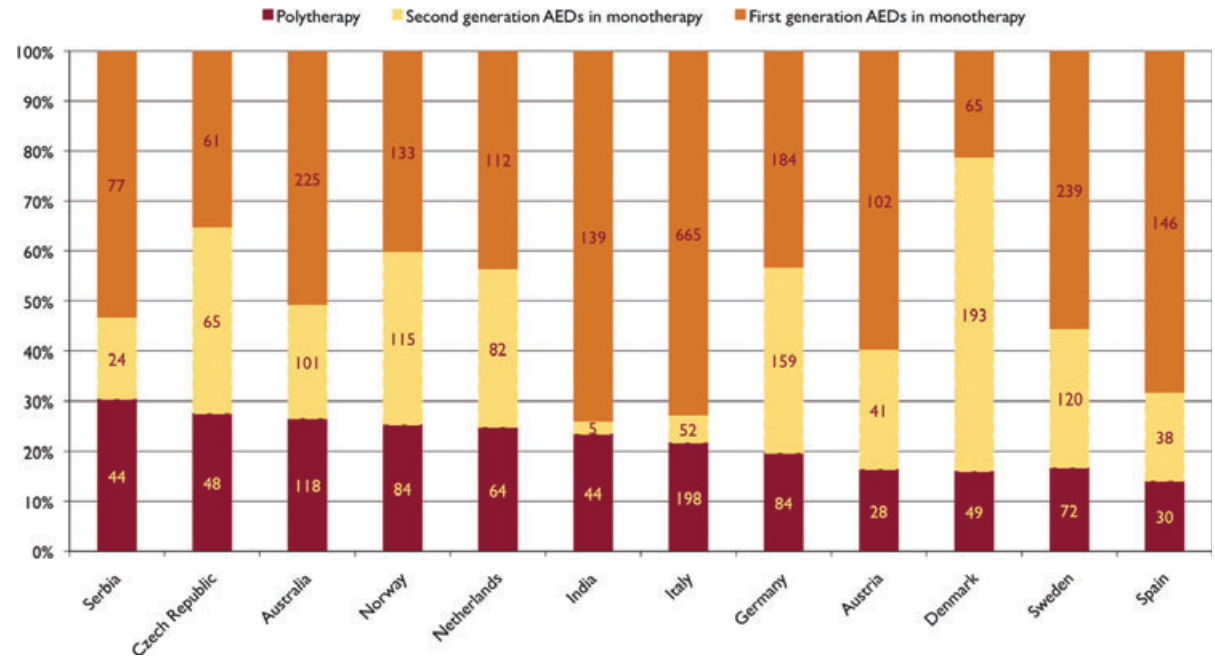

Figure 1.
Rates of exposure (%) to monotherapy with first- and second-generation antiepileptic drugs (AEDs), and to polytherapy, by country. Numbers in bars indicate number of pregnancies with each exposure. The following countries have each contributed <3% of all enrolled pregnancies or <2% of monotherapy exposures and are not included in the Figure: Argentina, Belgium, Chile, China, Croatia, Finland, Georgia, Hong Kong, Hungary, Israel, Japan, Lithuania, Macedonia, The Philippines, Slovakia, Slovenia, Switzerland, Taiwan, Turkey, United Kingdom. Taken together these countries account for a total of 792 pregnancies (17% of all).

The chi-square test was used to investigate the relationship between categories of AED exposure and the following covariates: (1) country of enrollment (countries accounting for <3% of enrolled pregnancies or with <2% of enrolled pregnancies exposed to monotherapy were pooled as "other countries"); (2) type of epilepsy (generalized or localization-related) (Commission on classification and terminology of the International League Against Epilepsy, 1989); (3) year of onset of pregnancy, defined by last menstrual period (≤2000, 2001, 2002, 2003, and ≥2004). Results are reported as odds ratios (OR) or means and 95% CIs. ORs related to each country were calculated using all other countries as the reference category, whereas ORs related to year of onset of pregnancy were calculated using onset of pregnancy in 2000 or earlier as reference.

Calculations were performed using JMP 6.0 for Macintosh (SAS Institute, Cary, NC, U.S.A.). Results were considered statistically significant for p-values <0.05 (two-sided); only statistically significant results are reported in the text.

Results

Monotherapy was used in 3,714 pregnancies (77.4%) and involved a second-generation AED in 1,139 (30.7%). Nineteen different AEDs were used in monotherapy, the most frequently prescribed being CBZ, VPA, and LTG (Table 1). A combination of two AEDs was prescribed in 919 pregnancies, three AEDs in 142, four AEDs in 19, and five AEDs in four. The most common combination was LTG with VPA (n = 144). The number of AEDs was increased in 117 pregnancies and a switch was made from one AED to another in 23.

Rates of exposure to monotherapy and to second-generation AEDs differed across countries (χ^2 59.4 and 640.5, respectively; $p < 0.0001$) (Fig. 1). Monotherapy was most frequent in Spain (OR 3.0; 95% CI 1.5–6.3; $p < 0.01$), Denmark (OR 2.2; 95% CI 1.2–4.0; $p < 0.01$), and Sweden (OR 2.0; 95% CI 1.2–3.2; $p < 0.01$), and least frequent in Australia (OR 0.6; 95% CI 0.4–0.9; $p < 0.05$) and Serbia/Montenegro (OR 0.4; 0.2–0.8; $p < 0.01$). Use of second-generation AEDs in monotherapy was highest

Table 1. Pregnancies exposed to monotherapy with individual antiepileptic drugs (AEDs) by country, number, and percentage of all exposures

	Individual AEDs in monotherapy						Other monotherapies	
Country	CBZ	LTG	VPA	PB	PHT	OXC	Second- generation AEDs	First- generation AEDs
Australia	115 (25.9)	85 (19.1)	86 (19.4)	1 (0.2)	12 (2.7)	1 (0.2)	15 (3.4)	11 (2.5)
Austria	46 (26.9)	26 (15.2)	52 (30.4)	2 (1.2)	0 (0.0)	3 (1.8)	12 (7.0)	2 (1.2)
Czech Republic	36 (20.7)	61 (35.1)	21 (12.1)	1 (0.6)	0 (0.0)	0 (0.0)	4 (2.3)	3 (1.7)
Denmark	27 (8.8)	149 (48.5)	24 (7.8)	0 (0.0)	0 (0.0)	32 (10.4)	12 (3.9)	14 (4.6)
Germany	75 (17.6)	138 (32.3)	85 (19.9)	5 (1.2)	7 (1.6)	11 (2.6)	10 (2.3)	12 (2.8)
India	49 (26.1)	2 (1.1)	57 (30.3)	11 (5.9)	20 (10.6)	3 (1.6)	0 (0.0)	2 (1.1)
Italy	276 (30.2)	29 (3.2)	173 (18.9)	159 (17.4)	11 (1.2)	10 (1.1)	13 (1.4)	46 (5.0)
The Netherlands	65 (25.2)	51 (19.8)	40 (15.5)	3 (1.2)	3 (1.2)	23 (8.9)	8 (3.1)	1 (0.4)
Norway	82 (24.7)	90 (27.1)	37 (11.1)	1 (0.3)	5 (1.5)	11 (3.3)	14 (4.2)	8 (2.4)
Serbia	44 (30.3)	24 (16.6)	27 (18.6)	6 (4.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Spain	80 (37.4)	29 (13.6)	49 (22.9)	10 (4.7)	6 (2.8)	6 (2.8)	3 (1.4)	1 (0. 5)
Sweden	130 (30.2)	105 (24.4)	84 (19.5)	0 (0.0)	18 (4.2)	5 (1.2)	10 (2.3)	7 (1.6)
Other countries	225 (28.4)	103 (13.0)	146 (18.4)	29 (3.7)	20 (2.5)	19 (2.4)	22 (2.8)	7 (0.9)
All countries total	1,250 (33.7)	892 (24.0)	881 (23.7)	228 (6.1)	102 (2.7)	124 (3.3)	123 (3.3)	114 (3.1)

Values are represented as n (%).

in Denmark (OR 50.4; 95% CI 29.1–89.1; $p < 0.0001$), the Czech Republic (OR 6.5; 95% CI 3.3–12.8; $p < 0.0001$), Norway (OR 4.3; 95% CI 2.6–7.1; $p < 0.0001$), Germany (OR 4.3; 95% CI 2.7–6.6; $p < 0.0001$), and The Netherlands (OR 3.1; 95% CI 1.7–5.4; $p = 0.0001$), and lowest in Italy (OR 0.035; 95% CI 0.020–0.060; $p < 0.0001$), India (OR 0.0074; 95% CI 0.0011–0.035; $p < 0.0001$), and Spain (OR 0.39; 95% CI 0.19–0.76; $p < 0.01$).

Exposure to individual AEDs in monotherapy (Table 1) also differed across countries (χ^2 1,216.7; $p < 0.0001$). In particular, PB accounted for 22.2% of all monotherapy exposures in Italy, whereas it was prescribed in less than 0.5% of cases in Australia, Denmark, Norway, and Sweden. Denmark had the lowest rate of exposure to VPA (9.3%) and the highest exposure to LTG (57.7%). High rates of LTG exposure were also recorded in the Czech Republic (48.4%) and Germany (40.2%), whereas LTG was used in less than 5% of pregnancies in Italy and India.

Monotherapy was associated more commonly with generalized epilepsies (1,643/2,040, 80.5%) than localization-related epilepsies (1,850/2,501, 73.9%) (OR 1.5; 95% CI 1.3–1.7; χ^2 27.5; $p < 0.0001$). Exposure to individual AEDs as monotherapy differed with diagnostic category (χ^2 881.4; $p < 0.0001$). Carbamazepine was prescribed in 15.3% of generalized versus 50.1% of localization-related epilepsies. The corresponding figures for other AEDs (generalized vs. localization-related) were: VPA, 42.2% versus 8.1%; LTG, 25.1% versus 21.7%; PB, 7.4% versus 5.3%; OXC, 1.0% versus 5.4%; PHT, 1.6% versus 3.9%.

The use of second-generation AEDs increased during the study period (χ^2 125.6; $p < 0.0001$). The OR for second-generation/first-generation AED exposure by year of onset of pregnancy was 0.6 (95% CI 0.4–0.9; $p < 0.01$) before 2001, 1.5 (95% CI 1.1–2.1; $p < 0.01$) in 2002, 2.1 (95% CI 1.6–2.7; $p < 0.0001$) in 2003, and 2.8 (95% CI 2.2–3,5; $p < 0.0001$) in 2004 or later. Exposure to individual AEDs also changed over time (χ^2 160.1; $p < 0.0001$): LTG exposures increased from 9.9% in pregnancies with onset before 2001 to 29.6% in those with onset after 2003, whereas over the same period CBZ exposures decreased from 39.9% to 31.5% and VPA exposures from 27.5% to 21.7% (Table 2).

Discussion

This report provides the first large-scale analysis of AED-utilization patterns during pregnancy in different regions, and demonstrates pronounced differences across countries and significant changes over time. Geographic differences were observed in rates of monotherapy exposure to second-generation AEDs, which ranged from 3.5% in India and 7.3% in Italy to 75% in Denmark. Although for India this can be explained by cost and availability constraints, differences in utilization of these drugs between Italy and Denmark are unlikely to be determined primarily by cost. This applies equally to the prominent differences in prescription rates of second-generation AEDs between Denmark (75%) and the Scandinavian neighbor countries Sweden (33%) and Norway (46%). With respect to individual AEDs, VPA was prescribed in only 9.3% of monotherapy exposures in Denmark, compared with 24% in the entire cohort from all countries. LTG contributed 58% of monotherapy exposures in Denmark and 48% in the Czech Republic, compared with an

Table 2. Exposure to individual antiepileptic drugs (AEDs) in monotherapy by year of onset of pregnancy

	Year of onset of pregnancy					
Individual AED in monotherapy	≤2000	2001	2002	2003	≥2004	Total
CBZ	186 (40)	200 (37)	225 (32)	264 (33)	375 (31)	1,250
LTG	46 (10)	95 (17)	173 (25)	225 (28)	353 (30)	892
VPA	128 (27)	138 (25)	173 (25)	184 (23)	258 (22)	881
PB	51 (11)	51 (9)	41 (6)	34 (4)	51 (04)	228
OXC	7 (2)	16 (3)	29 (4)	26 (3)	46 (4)	124
Other second-generation AEDs	11 (2)	11 (2)	19 (3)	29 (4)	53 (4)	123
Other first-generation AEDs	23 (5)	17 (3)	27 (4)	20 (2)	27 (2)	114
PHT	14 (3)	15 (3)	18 (3)	27 (3)	28 (2)	102
Total monotherapy AEDs	466	543	705	809	1,191	3,714

Values are represented as n (%). Number of pregnancies with the specified AED (n) and percentage of all monotherapies for that time period (%). CBZ, carbamazepine; LTG, lamotrigine; VPA, valproic acid; PB, phenobarbital; OXC, oxcarbazepine; PHT, phenytoin.

average of 24% in the total cohort. Denmark was the only country where OXC exceeded CBZ in exposures, possibly because OXC has been available for a longer time in Denmark than in most other countries (Tsiropoulos et al., 2006). Overall, these findings suggest that variation in prescribing patterns is related to local traditions and influences other than differences in costs and accessibility.

The apparent changes in prescription patterns over the years should be interpreted with caution, because the number of countries in the EURAP collaboration increased over time, and changes in AED utilization in the entire cohort might, therefore, reflect differences in drug use among countries that joined late. However, similar changes in prescription patterns were seen within countries that contributed data for the entire period (data not shown). The gradual increase in the prescription of second-generation AEDs, particularly LTG, is intriguing. This raises the possibility that some women were switched from first-generation AEDs to LTG, as also suggested by the parallel decrease in exposure to VPA and to CBZ. A shift from VPA could be in response to reports suggesting a high risk of birth defects associated with this drug (Wide et al., 2004; Artama et al., 2005; Wyszynski et al., 2005; Morrow et al., 2006; Vajda et al., 2006). However, available data do not indicate higher rates of birth defects with CBZ compared to LTG (Artama et al., 2005; Morrow et al., 2006).

There are limitations inherent to the EURAP methodology. First, the type of drug exposures may not reflect directly the physicians' preferred AED treatment for women of childbearing potential. Treatment may have been initiated years before conception, and women and their physicians may be unwilling to modify a previously successful treatment. Second, EURAP is not a population-based study. Only a fraction of eligible women are enrolled in the registry, and this proportion varies between countries. Our observations might not be representative of the general population of pregnant women with epilepsy, and observed exposure rates in individual countries may not reliably reflect differences in drug utilization at the national level. However, the observed differences in AED utilization between Denmark and Sweden in EURAP are reflected in these countries' national drug prescription databases of AED use in pregnant women [LTG most commonly used AED in pregnancy in Denmark (28%), followed by CBZ (20%), VPA (18%), and OXC (17%); CBZ most commonly used AED in Sweden (47%), followed by VPA (24%), LTG (19%), and very limited use of OXC (0.3%); National data for 2004].

In conclusion, our analysis reveals marked differences in how women with epilepsy are treated during pregnancy in different countries. There may be rational reasons for such variation, but local traditions and drug marketing activities are also likely to contribute. Most importantly, the pronounced differences in drug utilization across countries illustrate a lack of consensus, due to lack of an evidence base necessary for rational management of epilepsy in childbearing age. Hopefully, registries such as EURAP will fill some of the gaps concerning the relative safety of different AEDs during pregnancy. Geographic variation in patterns of drug exposure, however, may cause difficulties in generalizing reported associations of AED exposure and adverse pregnancy outcome from one region to another. The mechanisms behind occurrence of birth defects among offspring of women with epilepsy are likely to be multifactorial. Genetic predisposition, maternal epilepsy type, seizures during pregnancy, and several other factors might influence the teratogenic potential of AEDs (Perucca, 2005). Including such additional risk factors is essential in

any analysis of the relative risks for birth defects with specific AED exposures, particularly since these AEDs are used differently depending on the country in which the woman is treated.

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All members of the central project commission (CPC) of the EURAP study group listed below participated in the design of the study. The primary analysis was conducted by D.B. with assistance of E.B. T.T. and D.B. drafted the first version of the manuscript. All members participated in the interpretation of the data, contributed to the discussion, and reviewed and approved the final version of the manuscript. The members of the CPC of EURAP confirm that they read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Central project commission of EURAP: Dina Battino (Central Study Coordinator); Erminio Bonizzoni, John Craig, Dick Lindhout, Emilio Perucca, Anne Sabers, Frank Vajda, and Torbjörn Tomson (chair).

The other contributors and their respective roles in the study are listed in the appendix.

Disclosure: D.B. received speaker's fees from Sanofi-Aventis. J.C. received speaker's fees and funding for attending conferences from UCB, Sanofi-Synthelabo, Janssen-Cilag, Pfizer, and GSK. D.L. has received financial support for the BeNeLux part of the EURAP project from Janssen-Cilag, GSK, Pfizer, and UCB. E.P. received speakers' or consultancy fees and/or research grants from Bial, Eisai, GSK, Johnson & Johnson, Novartis, Pfizer, Sanofi-Aventis, UCB, and Valeant. A.S. received speaker's fees from UCB, Eisai, and Novartis. T.T. received speaker's fees and/or research grants from GSK, Sanofi-Aventis, Novartis, Janssen-Cilag, Pfizer, UCB, and Eisai. E.B. and F.V. have no conflicts of interest to declare.

Appendix I

Central project commission

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References

Artama M, Auvinen A, Raudaskoski T, Isojarvi I, Isojarvi J. (2005) Antiepileptic drug use of women with epilepsy and congenital malformations in offspring. *Neurology* 64:1874–1878.

Commission on Classification and Terminology of the International League Against Epilepsy. (1989) Proposal for revised classification of epilepsies and epileptic syndromes. *Epilepsia* 30:389–399.

Commission on Genetics, Pregnancy, and the Child International League Against Epilepsy. (1993) Guidelines for the care of women of childbearing age with epilepsy. *Epilepsia* 34:588–589.

EURAP Study Group. (2006) Seizure control and treatment in pregnancy: observations from the EURAP epilepsy pregnancy registry. *Neurology* 66:354–360.

Morrow J, Russell A, Guthrie E, Parsons L, Robertson I, Waddell R, Irwin B, McGivern RC, Morrison PJ, Craig J. (2006) Malformation risks of antiepileptic drugs in pregnancy: a prospective study from the UK Epilepsy and Pregnancy Register. *J Neurol Neurosurg Psychiatry* 77:193–198.

Perucca E. (2005) Birth defects after prenatal exposure to antiepileptic drugs. *Lancet Neurol* 4:781–786.

Tomson T, Perucca E, Battino D. (2004) Navigating toward fetal and maternal health: the challenge of treating epilepsy in pregnancy. *Epilepsia* 45:1171–1175.

Tsiropoulos I, Gichangi A, Andersen M, Bjerrum L, Gaist D, Hallas J. (2006) Trends in utilization of antiepileptic drugs in Denmark. *Acta Neurol Scand* 113:405–411.

Vajda FJ, Hitchcock A, Graham J, Solinas C, O'Brien TJ, Lander CM, Eadie MJ. (2006) Foetal malformations and seizure control: 52 months data of the Australian Pregnancy Registry. *Eur J Neurol* 13:645–654.

Wide K, Winbladh B, Kallen B. (2004) 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* 93:174–176.

Wyszynski DF, Nambisan M, Surve T, Alsdorf RM, Smith CR, Holmes LB. (2005) Increased rate of major malformations in offspring exposed to valproate during pregnancy. *Neurology* 64:961–965.

Supporting Information

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

Appendix S1. EURAP study group: Collaborators and their function.

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