EURAP

An International Antiepileptic Drugs and Pregnancy Registry

Interim Report Spain - May 2015

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BACKGROUND

All old-generation antiepileptic drugs (AEDs) are considered to be teratogenic and AEDs are among the most common causes of adverse effects to the foetus. The risks associated with the treatment of epilepsy during pregnancy is therefore of major concern to all women of childbearing potential with epilepsy. The information on the comparative teratogenicity of these AEDs in humans is, however, conflicting, mainly due to inadequate sample size and methodological differences between previous studies. The teratogenic potential of newer AEDs is even less known, a situation that prevents a rational approach to AED treatment in women of childbearing potential.

To address this problem, it is necessary to compile more information on outcome of pregnancies following maternal exposure to AEDs. Such information is needed to provide pre-pregnancy counselling concerning teratogenic risks, and possibilities for specific prenatal monitoring, including prenatal diagnosis of foetal disorders associated with specific medications. Given the current number of available AEDs and combinations, very large numbers of pregnancies have to be evaluated in order to establish the safety of each regimen. Large denominators are also needed because of the qualitative diversity of the main endpoint of outcome, major congenital malformations.

A number of independent groups with experience and interest in maternal and foetal well-being in association with maternal AED use have agreed on a prospective international multi-centre study of pregnancies with AEDs. Data from all participating groups are shared in a Central Registry of Antiepileptic Drugs and Pregnancy (EURAP). EURAP was established in the first centres in some European countries and has since then gradually expanded to include more centres and countries now involving also Asia, Oceania, Latin America and Africa.

OBJECTIVE OF EURAP

The primary objective of EURAP is to evaluate and determine the comparative risk of major foetal malformations following intake of AEDs (old and new) and their combinations during pregnancy.

METHODS

EURAP is a prospective and retrospective observational study. Women taking AEDs at the time of conception, irrespective of the indication, may be included. To avoid selection bias, only pregnancies recorded before foetal outcome is known and within week 16 of gestation are included in the prospective risk assessment. Cases ascertained later in pregnancy are recorded as retrospective cases, as they may provide signals, but are not included in the comparative risk evaluation.

Information on patient's demographics, type of epilepsy, seizure frequency, family history of malformations, drug therapy and of other potential risk factors is obtained, and follow-up data are collected once at each trimester, at birth and at one year after delivery.

Networks of reporting physicians have been established in countries taking part in the collaboration. During the course of the pregnancy, and the follow-up time after delivery, the participating physician enters data into five Subforms (Subforms A-E) for each patient.

Subform A is completed on enrolment of the patient, Subform B after the first trimester, Subform C after the second trimester, Subform D within three months after delivery, and Subform E within 14 months after birth. Immediately after completion, each Subform is submitted to the national coordinator for review. The national coordinator transfers the reviewed and accepted Subform to the Central EURAP Registry in Milan, Italy.

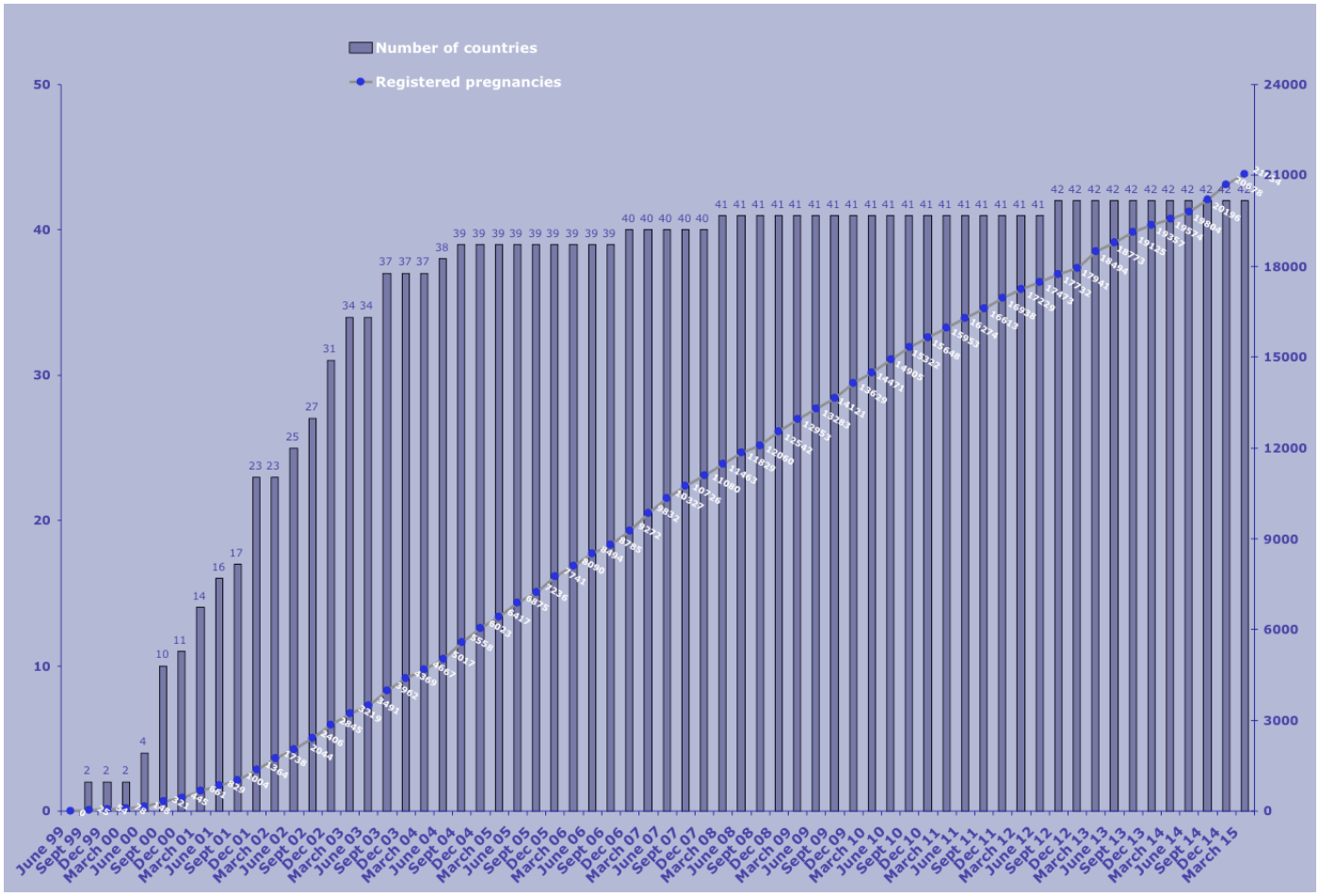
EVALUATION OF OUTCOME

The physician records descriptively abnormalities observed in the offspring. The final assessment and classification of the type of malformation is the responsibility of the Central Project Commission (CPC). In order to facilitate a uniform and objective assessment, reports of malformations are assessed regularly by an outcome assessment committee, which is kept blinded with respect to the type of exposure.

INTERIM REPORT

EURAP was implemented in the first two countries in Europe in 1999 and has since then grown rapidly with countries participating from Europe, Australia, Asia, South America and Africa. This development is reflected by increasing numbers of enrolled pregnancies. The development since 1999 is illustrated in Fig. 1.

Fig 1. Number of Participating Countries and Pregnancies Reported to the Central Registry by March 2015.



The present report is **based on data available in the Central Registry by May 13th, 2015**. At that time more than 900 reporting physicians from 42 countries had contributed cases to the Central Registry. Countries that had been active are listed in Table 1.

Table 1. Countries that have Contributed with Pregnancies Reported to the Central Registry of EURAP (n=42).

COUNTRY	National Coordinator (or referring physician*)	Date of joining the Registry
Albania	Jera Kruja*	2002
Argentina	Silvia Kochen	2002
Australia	Frank Vajda	2000
Austria	Gerhard Luef	2000
Belarus	Halina Navumava*	2008
Belgium	Dick Lindhout & Eugène van Puijenbroek	2002
Chile	Alejandro De Marinis	2002
China	Weiping Liao	2006
Croatia	Dinko Vitezic	2002
Czech Republic	Jana Zarubova & Irena Novotna	2001
Denmark	Anne Sabers	2000
Emirates	Istvan Ferencz *	2008
Finland	Reetta Kälviäinen	2003
France	Michel Baulac	2000
Georgia	Sofia Kasradze & Otar Toidze	2000
Germany	Bettina Schmitz	2000
Guatemala	Henry Stokes*	2003
Hong-kong	Patrick Kwan	2002
Hungary	Gábor Barcs	2001
India	Sanjeev Thomas	2001
Israel	Miri Neufeld	2000
Italy	Luigi M. Specchio	2000
Japan	Hideyuki Ohtani	2001
Lithuania	Ruta Mameniskiene	2002
Macedonia	Gordana Kiteva Trencevska	2001
Netherlands	Dick Lindhout & Eugène van Puijenbroek	2002
Namibia	Herbie Burmeister*	2012
Norway	Karl-Otto Nakken	2000
Philippines	Leonor Cabral-Lim	2003
Poland	Joanna Jedrzejczak	2001
Portugal	Isabel Pires* & Luis Isidoro* & Elia Baeta*	2001
Russia	Alla Guekht & Oksana Lokshina	2004
Serbia & Montenegro	Maja Milovanovic	2002
Slovakia	Vladimír Safcák	2002
Slovenia	Boštjan Čebular	2002
Spain	Meritxell Martinez Ferri	2001
Sweden	Torbjörn Tomson	2000
Switzerland	Barbara Tettenborn & Martin Kurthen	2001
Taiwan	Chi Wan Lai & Alice Yu	2004
Turkey	Çigdem Özkara & Demet Kinay	2000
Ukraine	Dmitriy Kovalenko*	2006
United Kingdom	John Craig & Aline Russell	2001

* referring physicians

By the cut-off date for this report (May 13th, 2015), **780 pregnancies from Spain** had been entered into the central database. Of these, **261 pregnancies are excluded** from the present interim report for reasons explained here below:

1. Pregnancies that failed to meet inclusion criteria (n= 2).
2. Lost to follow-up, including those failing to submit sub-forms within preset deadlines (n= 100).
3. Pending pregnancies, awaiting updates or corrections of different sub-forms (n= 23).
4. Ongoing pregnancies, updated and corrected (n= 4).
5. Retrospective, but completed and corrected (n=66). Among these, there are true retrospective pregnancies (n=63) and a further three pregnancies (n=3) that otherwise met our criteria for prospective pregnancies since they were recruited within 16th week, but which patients had an ultrasound examination performed before enrolment.
6. Retrospective, i.e. initially classified as prospective pregnancies but re-classified as retrospective cases because one or more CRF subforms were submitted after the set deadlines (n=45).
7. Unclassifiable i.e. cases for which it was impossible to determine if there was a malformation or not (n=1). This includes anomalies in 1 livebirth where the information was insufficient to determine if qualifying for malformation diagnosis or not *(the case reported a kidney dilatation with no information about the size of pelvic dilatation, and no treatment).*
8. Not yet classified, i.e pregnancies which classification is pending as well as pregnancies which became completed after the last time we sent the database to the OCC, regardless if they contained some malformations or not (n=2).
9. Treatment changes between different AEDs or mono- to polytherapy or vice versa during the first trimester (n=18).

Thus in total **519 prospective pregnancies** (enrolled at the latest during the 16th gestational week and before outcome is known) **are included** in this report.

The classification of the epilepsy among the prospective pregnancies is given in table 2. Epilepsy was the indication for treatment in all but 2 (0.4%) of the pregnant women.

Table 2. **Classification of the Epilepsy in 519 Prospective Pregnancies.**

Epilepsy	**N**	**%**
Localisation-related	319	61.5
Generalized	186	35.8
Undetermined	11	2.1
Missing information	1	0.2
No epilepsy	2	0.4
Total	**519**	**100**

The **maternal age** among prospective cases was 31.9 ±4.8 years (mean±SD), ranging from 17 to 46 years.

The women were of Caucasian **ethnicity** in 97.5% and of Other in 1.4%.

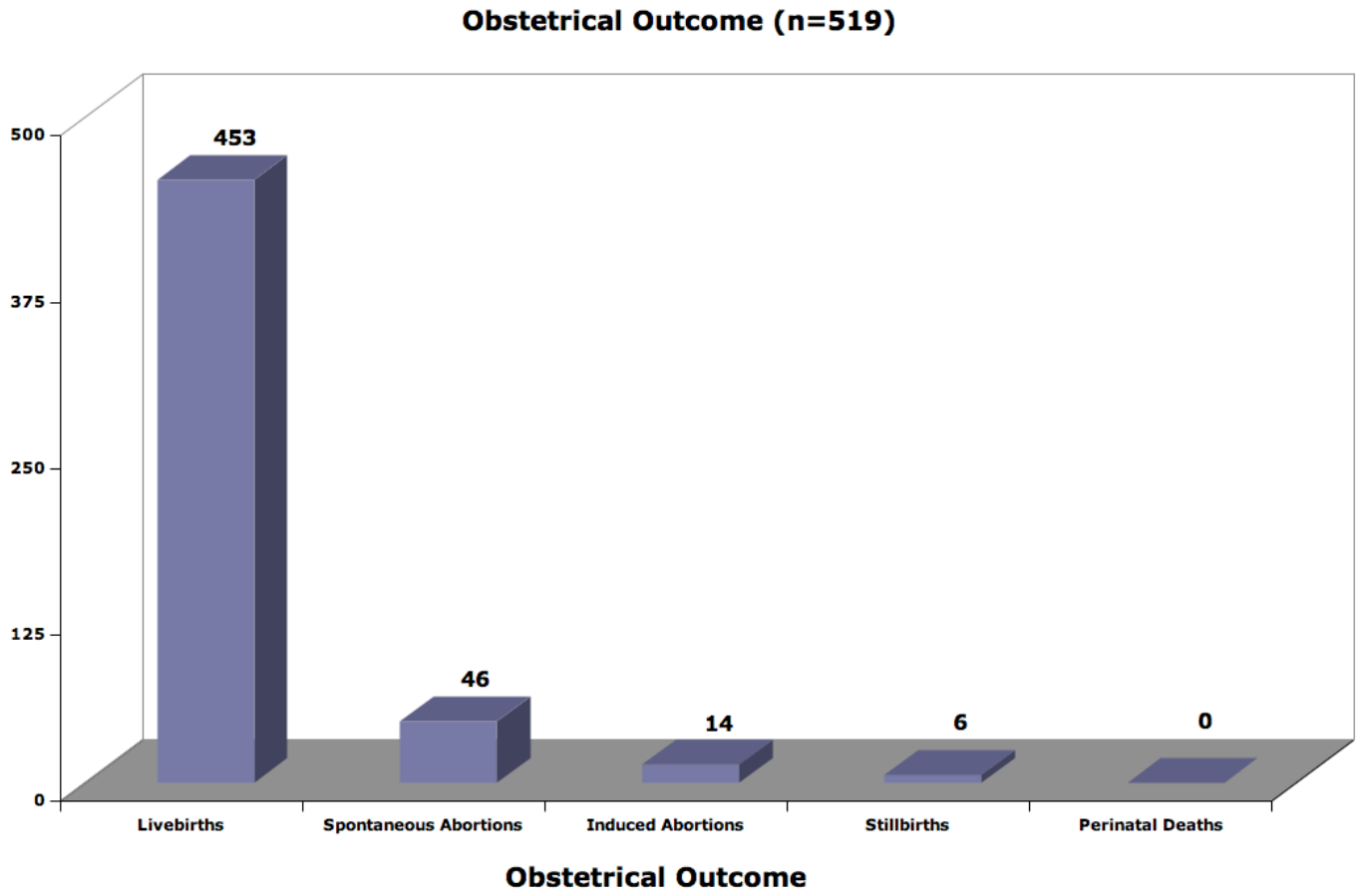
Gravida for each pregnancy is presented in Table 3.

Table 3. **Number of the Pregnancy in Prospective Cases.**

Gravida	**N**	**%**
1st pregnancy	250	48.2
2nd pregnancy	175	33.7
3rd pregnancy	66	12.7
4th pregnancy	23	4.4
5th pregnancy	4	0.8
> 5th pregnancy	1	0.2
Not ascertained	0	0.0
Total	**519**	**100**

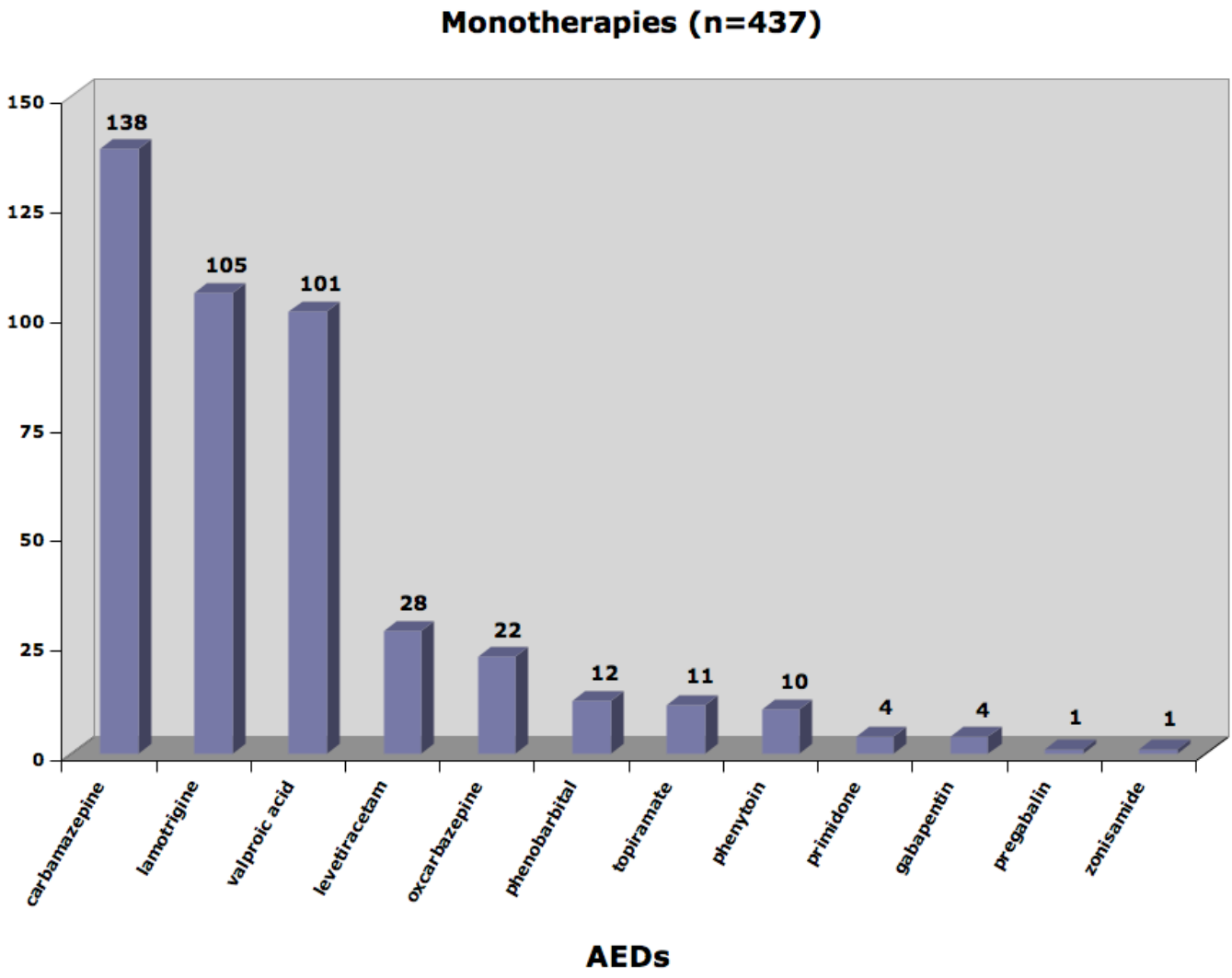
The outcome of the prospective completed pregnancies is presented in Figure 2. Out of the 14 induced abortions, 2 were for chromosomal abnormalities and/or syndromes and 4 were for other fetal indication detected by prenatal screening (*out of these 4 cases, 3 were finally confirmed as major malformations and 1 case was definitively classified as other abnormalities, as it refers to an empty egg with no embryo*). The remaining 8 induced abortion cases were due to maternal reasons (either medical or social).

Figure 2. Obstetrical Outcome of Prospective Pregnancies.



Of the pregnancies, 437 (84.2%) involved women on a single AED, 69 (13.3%) were on two AEDs whereas 13 (2.5%) took three AEDs or more. All women (100%) were on AED treatment during the 1st trimester. The exposure to the different AEDs in monotherapy among the prospective pregnancies is presented in Figure 3.

Figure 3. **Number of Prospective Pregnancies with Exposure to Different AEDs in Monotherapy.**



There were 41 different AED combinations. The most frequently used combinations were lamotrigine and valproic acid (n=9), lamotrigine and levetiracetam (n=6), carbamazepine and clobazam (n=6), lamotrigine and phenobarbital (n=4), carbamazepine and lamotrigine (n=4), levetiracetam and oxcarbazepine (n=4), clobazam and lamotrigine (n=3) and carbamazepine and levetiracetam (n=3) (Table 4).

Table 4. The Most Common AED Combinations.

The most common polytherapies	N
lamotrigine + valproic acid	9
lamotrigine + levetiracetam	6
carbamazepine + clobazam	6
lamotrigine + phenobarbital	4
carbamazepine + lamotrigine	4
levetiracetam + oxcarbazepine	4
clobazam + lamotrigine	3
carbamazepine + levetiracetam	3
carbamazepine + phenobarbital	2
topiramate + valproic acid	2
levetiracetam + topiramate	2
clonazepam + valproic acid	2
oxcarbazepine + valproic acid	2
carbamazepine + gabapentin	2
lamotrigine + phenytoin	2
clobazam + oxcarbazepine	2
clobazam + lamotrigine + valproic acid	2
carbamazepine + clobazam + lamotrigine + topiramate	2

The number of pregnancies with exposure to different new generation AEDs taken in combination with other AEDs are listed in Table 5.

Table 5. **Number of pregnancies with different new generation AEDs in combination therapy.**

Lamotrigine	38
Levetiracetam	21
Oxcarbazepine	14
Topiramate	12
Gabapentin	5
Pregabalin	1
Zonisamide	0
Vigabatrin	0
Tiagabine	0

TERATOGENIC OUTCOME

There were 29 major congenital malformations (MCM), none syndromic and/or monogenic case and 5 chromosomal abnormalities (CHR) in the prospective cohort of 473 pregnancies as shown in Table 6 (*46 spontaneous abortions are excluded*).

Table 6. Pathological Outcomes.

Outcome	Outcome Classification	N
MCM	Multiple major	4
	Isolated major	25
MCM		**29**
SYNDROMES or MONOGENIC CONDITIONS		**0**
CHR		**5**
Total		**34**

In this report we will confine our analysis to the 29 MCM including 3 induced abortions (none stillbirth and none neonatal death). Of the 26 live births, 4 cases of malformations were ascertained prenatally, 17 were first reported at birth and 5 within one year after birth.

Among the 29 cases with MCM, 7 were detected by ultrasound examination. Out of these 7, there were 3 induced abortions and 4 live births.

The 29 cases represent a **malformation rate of 6.1%** of all prospective pregnancies for which follow-up has been completed (29/473).

The type of malformations is described in Table 7.

Table 7

PATHOLOGICAL OUTCOMES	DESCRIPTION	N
MCM	Multiple major	**4**
	Nervous system	
MCM	Spina Bifida	3
	all	**3**
	Heart	
MCM	Ventricular septal defect	3
MCM	Aortic valve stenosis	1
MCM	Atrial septal defect	1
MCM	Patent ductus arteriosus	1
MCM	Coarctation of aorta	1
MCM	Transposition of great vessels (complete)	1
MCM	Hypoplastic left heart syndrome	1
	all	**9**
	Genital system	
MCM	Hypospadias	3
	all	**3**
	Musculoskeletal	
MCM	Hip dislocation and/or dysplasia	1
MCM	Congenital scoliosis due to congenital bony malformation	1
	all	**2**
	Limbs	
MCM	Club foot - talipes equinovarus	2
MCM	Polydactyly	1
	all	**3**
	Eye, ear, face and neck	
MCM	Other congenital corneal malformation	1
MCM	all	**1**
	Oro facial clefts	
MCM	Cleft lip, median	1
	all	**1**
	Urinary system	
MCM	Renal agenesis	3
	all	**3**
MCM	all	29
	Chromosomal	
CHR	Down's syndrome	3
CHR	Patau's syndrome	1
CHR	Karyotype 47,XXX	1
CHR	all	5
	Syndromes	
Syndromes or Monogenic Conditions	all	0
Total		**34**

In 22 out of 399 pregnancies with AED monotherapy one or more birth defects were observed (5.5%), as opposed to 7 out of 74 pregnancies with AED polytherapy (9.5 %) as shown in Table 8.

Table 8. *In this table, 46 spontaneous abortions have been excluded from the denominator.*

	No AED	**%**	**Monotherapy**	**%**	**Polytherapy**	**%**	**Total**
MCM	**0**	0.0	**22**	5.5	**7**	9.5	**29 (**6.1%**)**
CHR	**0**	0.0	**4**	1.0	**1**	1.3	**5 (**1.1%**)**
Syndromes	**0**	0.0	**0**	0.0	**0**	0.0	**0 (**0.0%**)**
No malformation	**0**	0.0	**373**	93.5	**66**	89.2	**439 (**92.8%**)**
Total	**0**	0	**399**	100	**74**	100	**473 (**100%**)**

Outcome regarding the four most common monotherapies has been published in Lancet Neurology, June 6, 2011. Outcome in relation to exposure to individual drugs or specific drug combinations is not included in the present report.

ORGANISATION, FUNDING AND SUPPORT.

EURAP is a consortium of independent research groups working on a non-profit basis. The project is administratively organised by the Central Project Commission (CPC) with members representing different geographical areas and disciplines. The project has been supported by educational grants to the CPC from Eisai Pharmaceuticals, GlaxoSmithKline, Janssen-Cilag, Johnson & Johnson, Pfizer, Bial, Sanofi-Synthelabo, Novartis and UCB Pharma. In addition, national and regional networks may receive support from the same or other pharmaceutical companies.

APPENDIX

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