

North American AED Pregnancy Registry:

Comparative Safety of Some Anticonvulsant Polytherapies

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<http://www.AEDPregnancyRegistry.org>

Anticonvulsant Drugs

"OLD"

Phenobarbital (1912)

Phenytoin (Dilantin, 1938)

Trimethadione (Tridione, 1946)

Paramethadione (Paradione, 1949)

Primidone (Mysoline, 1954)

Carbamazepine (Tegretol, 1974)

Clonazepam (Klonopin, 1975)

Valproic Acid (Depakote, 1978)

"NEW"

Felbamate (Felbatol, 1993)

Gabapentin (Neurontin, 1993)

Lamotrigine (Lamictal, 1994)

Topiramate (Topamax, 1996)

Levetiracetam (Keppra, 1999)

Oxcarbazepine (Trileptal, 2000)

Zonisamide (Zonegran, 2000)

Pregabalin (Lyrica, 2005)

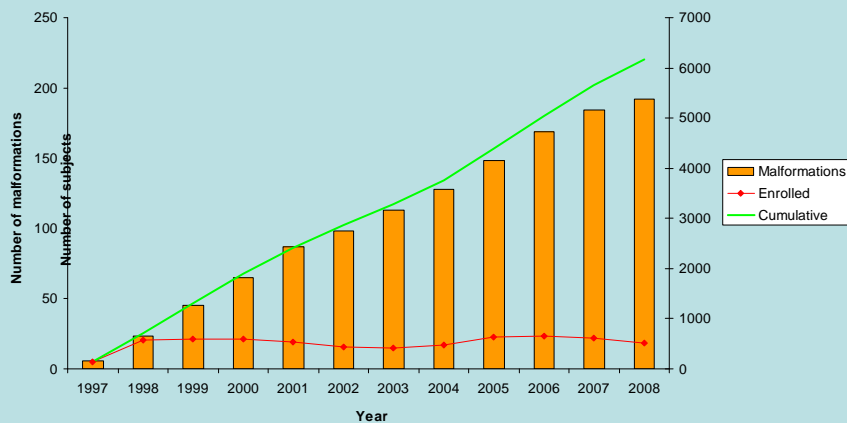
Vigabatrin (Sabril)

North American AED (antiepileptic drug) Pregnancy Registry: 1-888-233-2334 (toll-free)

STEPS:

- Woman must make initial call
- Informed Consent in interview
- Three interviews: Enrollment (10-15 min.)
 - 7 Months GA (5 min.)
 - 2 Months postpartum (5 min.)
- Written consent obtained for her and infant's medical records
- Findings in infant reviewed to include or exclude
- Major malformations reported to manufacturer
- Release of findings with approval of scientific advisors

Background



AED Pregnancy Registry

Pregnancy Registries: Hospital-Based

**North American AED (antiepileptic drug)
Pregnancy Registry: 1-888-233-2334 (toll-free)
<http://www.AEDPregnancyRegistry.org>**

- **Established in 1997 at Massachusetts General Hospital, Boston**
- **As of May 1, 2009, we have enrolled 6,579 pregnant women**

80% monotherapy

62% “pure” prospective

23 different monotherapies

204 different drug polytherapy regimens

425 controls

North American AED Pregnancy Registry: Major Malformations

**INCLUDE: Structural abnormality with surgical
medical or cosmetic importance**

**ISSUES: Mother’s description and written
permission**

Teratologist makes judgment

Decision tree maintains consistency

No master list is possible

**Range of severity: lethal, handicapping
moderate fixable and mild**

North American AED Pregnancy Registry: Exclusions

MINOR ANOMALIES:	preauricular sinus, simian crease
BIRTH MARKS:	hemangioma, congenital mole
PREMATURITY RELATED:	undescended testes, PDA
GENETIC DISORDERS:	Down Syndrome, achondroplasia, polydactyly, postaxial, type B
POSITIONAL DEFORMITY:	hip dysplasia with breech
ULTRASOUND ONLY:	unilateral renal agenesis
TECHNOLOGY INDUCED:	muscular VSDs tiny ASD (<0.4 mm)

Ungar L et al: Birth Def Res (Part A): 76:373, 2006
PB (n=77) and VPA (n=149): 16% had features excluded

Comparison Populations:

- 1. Active Malformations Surveillance Program, BWH:
1972 – 2000: 207,224 livebirths, stillbirths and
elective terminations for anomalies
- time period: birth to 5 days of age**

REF: Nelson K, Holmes LB: N Engl J Med 320:19-23, 1989.
Peller A et al: Obstet Gynecol 104 (5):957-964, 2004.

- 2. Friends and family members of enrolled women:
425 to date; demographic features very similar to
enrolled**

Power Calculations

Malformation rate In population <u>Example)</u>	<u>Rate Ratio</u>	Number needed for <u>80% power</u>
2%	2	555
(All malformations)		
1%	2	1127
(Heart defect)	3	360
	4	192
0.1%	3	3655
(Cleft lip/palate; Spina bifida)	5	1281
	7	722
	10	418
0.02%	5	6418
(Renal agenesis)	10	2097
	25	617
	40	345

Update – Major Congenital Anomalies

Prevalence of major malformations among infants exposed to phenobarbital*, valproate, lamotrigine, or carbamazepine as monotherapy during the first trimester. Both pure and traditional prospective exposures. Published.**

	Phenobarbital* (n = 77)	Valproate** (n = 149)	Lamotrigine*** (n = 684)	Carbamazepine (n=901)
Child with Confirmed Major Congenital Anomaly ¹	5 (6.4%) (2.1 to 14.5%)	16 (10.7%) (6.3 to 16.9%)	16 (2.3%) (1.3 to 3.8)	22 (2.4%) (1.6 to 3.6%)
Relative risk (95%CI)	4.2 (1.5 to 9.4)	7.3 (4.4 to 12.2)	1.4 (0.9 to 2.3)	1.5 (1.0 to 2.3)

* Holmes LB et al. Arch Neurol 2004;61:673-678.

** Wyszynski DF et al. Neurology 2005;64:961-965.

***Holmes LB et al: Neurology 2008; 70:2152-2158.

¹ Confirmed by inspection of medical records or interviews with pediatricians by experienced clinical dysmorphologists.

Study population

Characteristics of women and newborns exposed to lamotrigine and carbamazepine during the 1st trimester.

	Lamotrigine		Carbamazepine	
	Monotherapy (n = 1233)	Polytherapy (n = 398)	Monotherapy (n = 1009)	Polytherapy (n = 297)
Child Male	606 (50.4)	202 (51.7)	511 (51.2)	162 (56.1)
Married	996 (89.7)	235 (77.8)	376 (82.6)	105 (72.9)
Mother's Education				
≤Grade 12	145 (13.1)	81 (26.8)	83 (18.1)	40 (27.8)
Some College, Junior Graduate	238 (21.4)	76 (25.2)	99 (21.6)	45 (31.3)
College Graduate (4-year)	446 (40.1)	105 (34.8)	172 (37.5)	44 (30.6)
Post College	282 (25.4)	40 (13.3)	105 (22.9)	15 (10.4)
Maternal Age (mean, SD)	29.9 (5.1)	28.8 (5.4)	29.7 (5.5)	29.4 (5.1)
Gravida (mean, SD)	2.0 (1.3)	2.0 (1.2)	2.2 (1.3)	2.3 (1.5)
Mother Caucasian	1095 (88.8)	346 (86.9)	885 (87.7)	237 (79.8)
Father Caucasian	1048 (85.2)	317 (79.7)	853 (84.7)	226 (76.4)

Major Congenital Anomalies

Prevalence of major malformations among infants exposed to lamotrigine during the first trimester. Both pure and traditional prospective exposures.

	Lamotrigine			
	Monotherapy (n = 1233)	Polytherapy		
		Valproate (n = 42)	Phenobarbital (n = 31)	Carbamazepine (n = 85)
Child with Confirmed Major Congenital Anomaly¹	19 (1.5%) (1.0 to 2.4%)	4 (9.5%) (3.1 to 21.4%)	1 (3.2%) (0.2 to 14.9%)	3 (3.5%) (0.89 to 9.3%)
Relative risk (95%CI)²	0.95 (0.61 to 1.5)	5.9 (2.3 to 15.0)	2.0 (0.3 to 13.7)	2.2 (0.7 to 6.6)

¹Confirmed by inspection of medical records or interviews with pediatricians by experienced clinical dysmorphologists.

² Using the baseline prevalence rate of 1.62% in the unexposed comparison group. Active Malformations Surveillance Program at Brigham and Women's Hospital in Boston (n=69,277).

Major Congenital Anomalies

Prevalence of major malformations among infants exposed to lamotrigine during the first trimester. Both pure and traditional prospective exposures.

	Lamotrigine			
	Monotherapy (n = 1233)	Polytherapy		
		Valproate (n = 42)	Non-Valproic (n = 356)	
Child with Confirmed Major Congenital Anomaly¹	19 (1.5%) (1.0 to 2.4%)	4 (9.5%) (3.1 to 21.4%)	9 (2.5%) (1.2 to 4.6%)	
Relative risk (95%CI)²	0.95 (0.61 to 1.5)	5.9 (2.3 to 15.0)	1.6 (0.8 to 3.0)	

¹Confirmed by inspection of medical records or interviews with pediatricians by experienced clinical dysmorphologists.
² Using the baseline prevalence rate of 1.62% in the unexposed comparison group. Active Malformations Surveillance Program at Brigham and Women's Hospital in Boston (n=69,277).

Major Congenital Anomalies

Prevalence of major malformations among infants exposed to carbamazepine during the first trimester. Both pure and traditional prospective exposures.

	Carbamazepine			
	Monotherapy (n = 1009)	Polytherapy		
		Valproate (n = 28)	Non-Valproic (n = 269)	
Child with Confirmed Major Congenital Anomaly¹	22 (2.1%) (1.4 to 3.2%)	4 (14.2%) (4.7 to 31.0)	5 (1.9%) (0.7 to 4.1)	
Relative risk (95%CI)²	1.3 (0.89 to 2.0)	8.8 (3.6 to 21.9)	1.1 (0.5 to 2.7)	

¹Confirmed by inspection of medical records or interviews with pediatricians by experienced clinical dysmorphologists.
² Using the baseline prevalence rate of 1.62% in the unexposed comparison group. Active Malformations Surveillance Program at Brigham and Women's Hospital in Boston (n=69,277).

Polytherapies: Major Malformations

	RATE
CBZ + VPA (n = 62)	8.8% (95CI:3.8-18.9%)
LTG + VPA (n=141)	9.6% (95CI:5.7-15.7%)
CBZ + LTG (n=118)	0% (95CI:0.0-3.3%)
Morrow J et al: J Neurol Neurosurg Psych 77:193-198, 2006	
LTG + VPA (n=88)	12.5% (95CI:6.7-21.7%)
LTG + non-VPA (n=182)	2.7% (95CI:1.0-6.6%)
Cunningham M et al: Neurology 64:955-960, 2005	

North American AED Pregnancy Registry

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AED Pregnancy Registry: Decisions to Release

SCIENTIFIC ADVISORY COMMITTEE:

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Major Congenital Anomalies

Prevalence of major malformations among infants exposed to lamotrigine or carbamazepine during the first trimester. Both pure and traditional prospective exposures. Internal control group.

	Lamotrigine		Carbamazepine	
	Monotherapy (n = 1233)	Polytherapy (n = 398)	Monotherapy (n = 1009)	Polytherapy (n = 297)
Child with Confirmed Major Congenital Anomaly¹	22 (1.8%) (1.1 to 2.6%)	15 (3.8%) (2.2 to 6.0%)	28 (2.8%) (1.9 to 3.9%)	9 (3.0%) (1.5 to 5.5%)
Relative risk (95%CI)²	1.0 (0.4 to 2.5)	2.1 (0.84 to 5.4)	1.6 (0.66 to 3.8)	1.7 (0.62 to 4.8)

1 Confirmed by inspection of medical records or interviews with pediatricians by experienced clinical dysmorphologists. Diagnosed before 12 weeks after delivery.
2 Using as the reference the internal control group of unexposed women, prevalence rate of 1.8% (6/340).