Epilepsie : spécificité de la prise en charge dans la contraception et la grossesse

S Dupont
Unité Epileptologie
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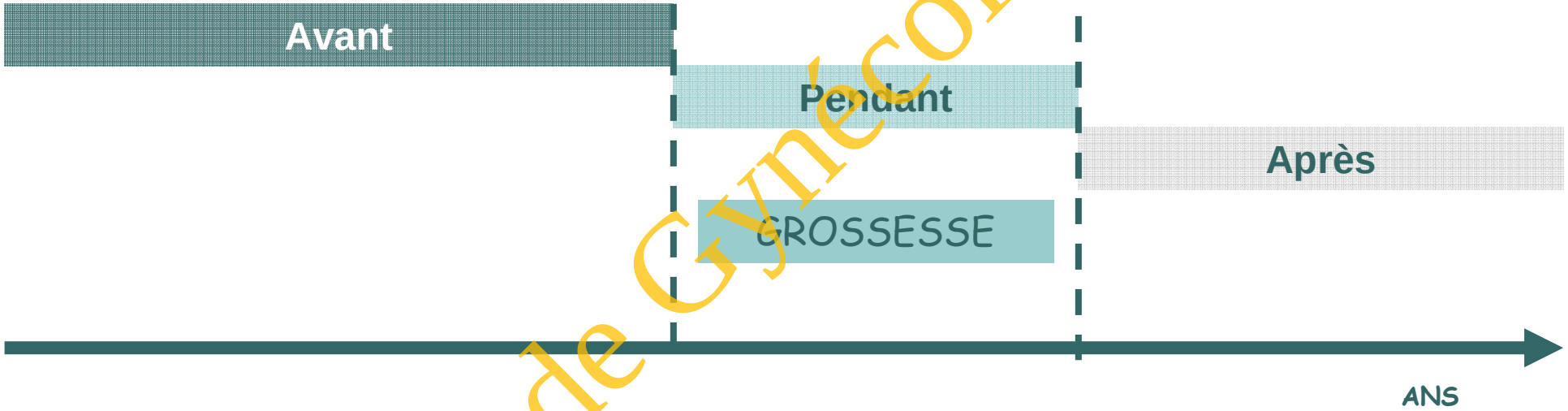
Liens d’intérêt

- Le Pr S Dupont a reçu en tant que consultante et oratrice des honoraires des laboratoires EISAI & UCB



Maîtrise grossesse: contraception

Planification/Information grossesse

Gestion MAE

Gestion épilepsie

Coordination

Suivi renforcé

Rééquilibration MAE

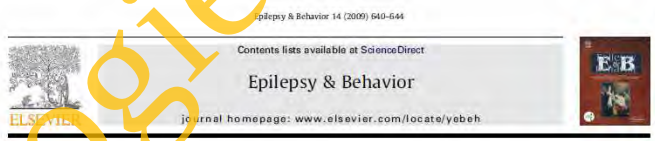
Allaitement

Suivi devenir enfants

Quelle contraception?

- 65% des patientes épileptiques Américaines traités par un MAE inducteur enzymatique ignoraient que leur traitement antiépileptique réduisait l'efficacité de leur contraception

- Une grossesse non programmée sur quatre serait liée à l'inefficacité de la méthode contraceptive prescrite chez les patientes épileptiques Américaines



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Antiepileptic drugs: Are women aware of interactions with oral contraceptives and potential teratogenicity?

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Population based, prospective study of the care of women with epilepsy in pregnancy

Susan D Fairgrieve, Margaret Jackson, Patricia Jonas, David Walshaw, Kathleen White, Tara L Montgomery, John Burn, Sally A Lynch

This prospective, population based study in the former Northern health region was designed to establish the proportion of pregnant women with a history of epilepsy; doctors supervising their care; effectiveness of preconceptional counselling and control of epilepsy; and use of medication and pregnancy outcomes.

Subjects, methods, and results

The project had approval from regional ethics committees. Pregnant women with epilepsy were recruited to the study, predominantly by community midwives. Women who consented were interviewed by using a standard questionnaire. Hospital notes were reviewed after the women had given birth. General practice and hospital notes were checked in one area to confirm the women's response regarding preconceptional advice. Between 1 January 1997 and 31 December 1998, 400 notifications of pregnancies to women with epilepsy were received (the total number of livebirths, stillbirths, and medical terminations for this period was 65 478, giving a proportion of all pregnancies to women with epilepsy of 6.1/1000).

Three hundred women were interviewed, 60 did not consent to interview, contact was unsuccessful for 36, and 4 were notified retrospectively. Epilepsy management was undertaken by general practitioners in 182/300 (61%) women; 214/300 (71%) reported ongoing seizures; and 53/252 (21%) women taking antiepileptic drugs reported no seizures for >2 years. A history of epilepsy was reported by 48 women who no longer took antiepileptic drugs. Of the remaining 252, 210 (83.3%) were on monotherapy, most often carbamazepine (52%) and sodium valproate (35%). The diagnosis of epilepsy was questionable in 16/300 (5%) women. Incomplete compliance with medication was reported by 157/252 (62.3%) women.

Only 113/300 (38%) women recalled receiving preconceptional counselling. However, review of the notes of 25 women who denied having received advice showed that 8 (32%) had been counselled. Less than 50% (88/199) planned their pregnancies and 27/111 reported oral contraceptive failure. Only 32 (11%) took folate appropriately.

Of the 359/400 known pregnancy outcomes there were 330 live births (three sets of twins); two medical terminations, two stillbirths, 22 miscarriages, and five terminations.

The obstetric complication rate and mode of delivery were similar to that of the background population

Quelle contraception?

Journal of Midwifery & Women's Health www.jmwh.org
Clinical Rounds

Contraception and Antiepileptic Drugs

Taasha Guillemette, WHNP-BC, CRNP, MSN, MA, Susan M. Yount, CNM, PhD, WHNP-BC

Attention aux inducteurs enzymatiques !

Table 1. Recommendations for Use of Hormonal Contraceptives and Enzyme-inducing AEDs from the *US Medical Eligibility Criteria for Contraceptive Use* and Expert Opinion

	US Medical Eligibility Criteria for Contraceptive Use Category[a]				
EI-AEDs	COCs, Contraceptive Patch (Evra) and Ring (NuvaRing)[b]	POP[b]	Progestin Implant (Implanon)[b,c]	DMPA Injection (Depo-Provera)[d]	LNG-IUS (Mirena)[d]
Carbamazepine (Tegretol)	3	3	2	1	1
Felbamate (Felbatol)	NA	NA	NA	NA	NA
Oxcarbazepine (Trileptal)	3	3	2	1	1
Phenobarbital	NA	NA	NA	NA	NA
Phenytoin (Dilantin)	3	3	2	1	1
Primidone (Mysoline)	3	3	2	1	1
Topiramate (Topamax)	3	3	2	1	1
Rufinamide (Banzel)	NA	NA	NA	NA	NA
Lamotrigine (Lamictal)	3	1	1	NA	1

MAE	INDUCTEURS	INHIBITEURS	NEUTRES
Carbamazepine	●●●		
Eslicarbazepine	●●		
Felbamate	● Pour OP	●●●	
Gabapentine			●●●
Lacosamide			●●●
Lamotrigine			●●●
Levetiracetam			●●●
Oxcarbazepine	●●		
Perampanel			●● < 10 mg/j
Phenobarbital	●●●		
Phenytoine	●●●		
Pregabaline			●●●
Rétigabine			●●●
Rufinamide			●●●
Tiagabine			●●●
Topiramate	● < 200 mg/j		● < 200 mg/j
Valproate		●●●	
Vigabatrin			●●●
Zonisamide			●●●

● Ancienne génération

● Nouvelle génération

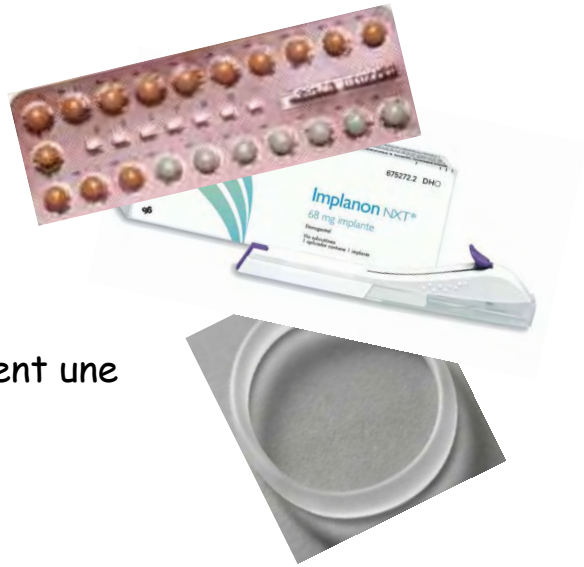
Quelle contraception?

Méthodes contraceptives dont l'efficacité n'est pas modifiée par les inducteurs enzymatiques.

DIU au levonorgestrel
DIU au cuivre
Methodes barrieres
Acetate de medroxyprogesterone injectable (DMPA)

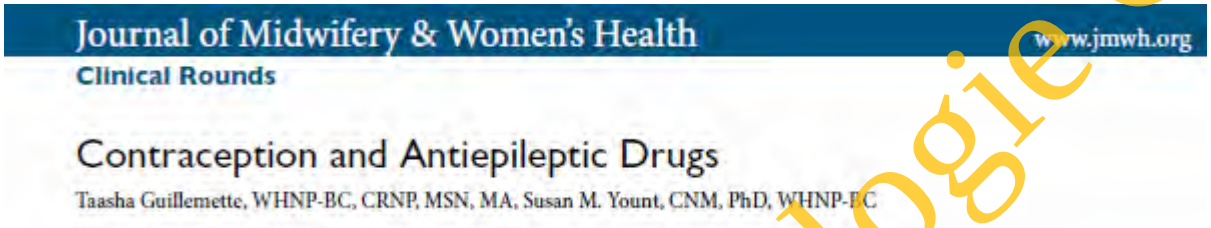
Méthodes contraceptives dont l'efficacité est modifiée par les inducteurs enzymatiques.

Contraception estroprogestative orale/patch/anneau
Microprogestatifs
Implant à l'etonogestrel
Macroprogestatifs*



* Il n'existe aucune étude sur leur efficacité en cas de prise de MAE inducteurs enzymatiques, mais les études pharmacocinetiques suggérent une baisse d'efficacité

Contraception du lendemain?


Journal of Midwifery & Women's Health
www.jmwh.org
Clinical Rounds

Contraception and Antiepileptic Drugs

Taasha Guillemette, WHNP-BC, CRNP, MSN, MA, Susan M. Yount, CNM, PhD, WHNP-BC

Pose d'un DIU au cuivre dans les 5 jours qui suivent le rapport non protégé+++

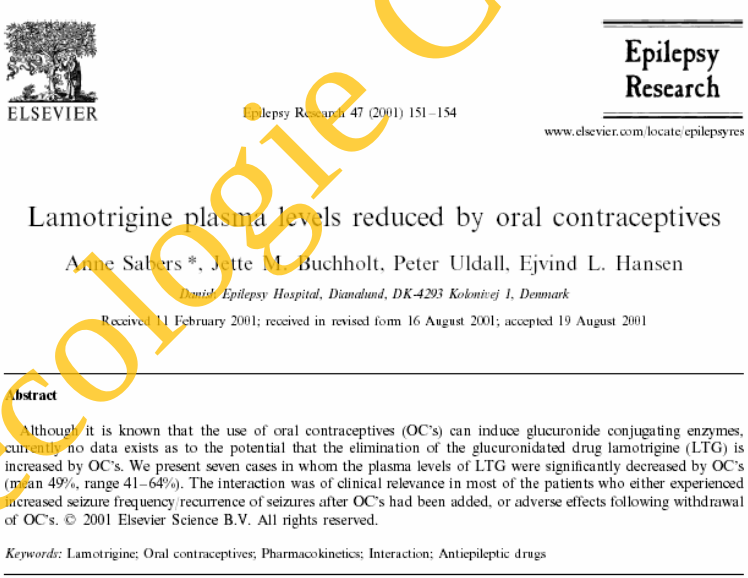
Pilule du lendemain: ulipristal acetate tablet, 30 mg (ella)
agoniste/antagoniste de la progestérone:

- études cliniques rapportant une baisse de concentration plasmatique si prise de médicaments inducteurs du CYP3A4 (ex: phénytoïne) mais pas cytochrome P450
- pas de recul si MAE inducteur enzymatique cytochrome P450
- proposition doubler les doses mais efficacité???

Cas de la lamotrigine

Diminution des taux plasmatiques de lamotrigine sous COC pouvant entraîner une potentielle recrudescence des crises

Pas d'impact des progestatifs purs sur les taux plasmatiques de lamotrigine



ELSEVIER

Epilepsy Research 47 (2001) 151–154

Epilepsy Research

www.elsevier.com/locate/epilepsyres

Lamotrigine plasma levels reduced by oral contraceptives

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Received 11 February 2001; received in revised form 16 August 2001; accepted 19 August 2001

Abstract

Although it is known that the use of oral contraceptives (OC's) can induce glucuronide conjugating enzymes, currently no data exists as to the potential that the elimination of the glucuronidated drug lamotrigine (LTG) is increased by OC's. We present seven cases in whom the plasma levels of LTG were significantly decreased by OC's (mean 49%, range 41–64%). The interaction was of clinical relevance in most of the patients who either experienced increased seizure frequency/recurrence of seizures after OC's had been added, or adverse effects following withdrawal of OC's.

Keywords: Lamotrigine; Oral contraceptives; Pharmacokinetics; Interaction; Antiepileptic drugs

0.3-0.5 % des femmes enceintes sont épileptiques → 4000 à 5600 femmes enceintes épileptiques/an en France

Olafsson et al. 1998, Viinikainen et al. 2005

1.Mes médicaments et mon bébé?

2.Mon épilepsie?

3. Allaitement?

Risques:

Tératogénicité?
Devenir cognitif?
Devenir comportemental ?
Autres?

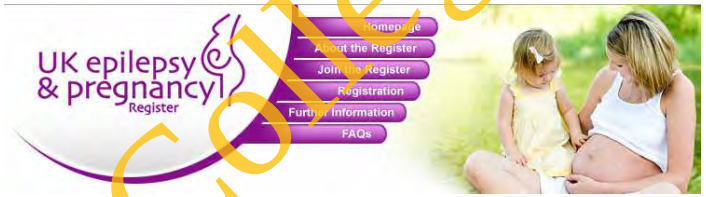
Gestion:

Equilibre
Effet des crises
Surveillance

Risques	**tératogénicité**	cognition	comportement	autres

Crée en 1999 / 42 pays
22 912 inclusions en 2017
Estimation à J0 et à 1 an

Crée en 1997
10 200 inclusions en 2016
Vs taux malformations population contrôle (registre Brigham): 1.62%
Estimation entre J0-J5



Crée en 1996
10 766 inclusions en 2016
Estimation à naissance

Le cas du Valproate de sodium

FORMULAIRE D'ACCORD DE SOINS
TRAITEMENT DES PATIENTES PAR VALPROATE

Document à remplir et à signer

L'objectif de l'accord de soins est de garantir que les patientes qui sont en âge ou vont être en âge d'être enceintes (en âge de procréer) soient pleinement informées et comprennent les risques de malformations congénitales et de troubles neurodéveloppementaux chez les enfants nés de femmes ayant pris du valproate pendant la grossesse.

Cet accord de soins doit être complété par le médecin spécialiste et par chaque patiente, avant le début de l'instauration de son traitement par valproate et à chaque réévaluation de celui-ci (au minimum lors de chaque prescription annuelle).

Il doit être présenté à la pharmacie pour toute délivrance du médicament.

Informations sur la patiente

Nom : _____ Prénom : _____

Si patiente mineure et/ou protégée par la loi, nom de son représentant* _____

A CONFIRMATION PAR LE MÉDECIN PRESCRIPTEUR

- Je confirme que la patiente susnommée présente une réponse insuffisante ou une intolérance aux autres traitements et que le valproate est la seule option thérapeutique. ☐

J'ai discuté des points suivants avec la patiente susnommée/son représentant* :

- Les enfants nés de mères exposées au valproate pendant la grossesse, présentent un risque élevé de malformations congénitales (environ 10 %) et un large éventail de troubles neurodéveloppementaux dont des troubles du spectre autistique (jusqu'à 30 % à 40 %) susceptibles d'entraîner des troubles importants de l'apprentissage. ☐
- La nécessité d'utiliser la dose minimale efficace. ☐
- La nécessité d'une contraception efficace (si la patiente est en âge de procréer). ☐
- La nécessité de réévaluer régulièrement le traitement, au moins une fois par an, et si la patiente envisage une grossesse. ☐
- La nécessité de consulter en urgence si la patiente est enceinte ou pense l'être pendant le traitement. ☐
- J'ai remis un exemplaire de la brochure d'information patient à la patiente elle-même/son représentant.* ☐

Nom du prescripteur : _____ Date : _____

Signature et tampon : _____

B POUR LA PATIENTE/SON REPRÉSENTANT

Veuillez lire attentivement ce qui suit et cocher la case correspondante pour confirmer votre accord.

Je soussigné(e) _____ comprends :

- Que le traitement par valproate m'est prescrit car je présente une réponse insuffisante ou une intolérance aux autres traitements et que le valproate est la seule option thérapeutique. ☐
- Que les enfants nés de mères exposées au valproate pendant la grossesse présentent un risque élevé de malformations congénitales (environ 10 %) et de nombreux types de troubles neurodéveloppementaux dont des troubles du spectre autistique (jusqu'à 30 % à 40 %). ☐
- Que si je suis en âge de procréer, je dois utiliser une contraception efficace. ☐
- Que je n'envisage pas de grossesse. ☐
- Que mon traitement sera réévalué régulièrement et au moins une fois par an. ☐
- Que je dois demander une consultation AVANT d'envisager de concevoir un enfant. ☐
- Qu'en cas de grossesse ou si je pense être enceinte pendant le traitement par valproate, je dois consulter immédiatement mon médecin. ☐

Nom de la patiente/représentant* : _____ Date : _____

World Report

France steps up warning measures for valproate drugs

Last week, France attempted to correct its past mishandling of concerns about sodium valproate drugs for epilepsy in pregnancy with a raft of new steps. Barbara Casassus reports from Paris.

French Health Minister Marisol Touraine has issued a new series of measures to help ensure that no more women of childbearing age take sodium valproate drugs without being fully aware of the potential dangers to their unborn babies.

The move came after a report from the general inspectorate for social affairs (IGAS) last month criticised the authorities and lead drug company Sanofi for not reacting more rapidly when congenital malformations and then development disorders started to be linked to Sanofi's Dépakine, three valproate derivatives, and generic drugs that are prescribed to prevent epilepsy and bipolar seizures.

The drug, which was launched in France in 1967, has probably caused malformations in about 450 children born between 2006 and 2014, according to IGAS. The first scientific indications of the problem appeared in 1982, whereas those for neurodevelopmental difficulties emerged much later, from 2000. Formal proof of the latter was established in 2011, and now it is estimated that 40% of the children exposed to valproate had a 10-point lower than average IQ at the age of linked to valproate and other drugs from the local register in the Rhône-Alpes region in southern France, and create a legal expert mission to determine compensation for victims based on the lack of information and damages caused. All this comes on top of earlier steps taken by the ministry's health directorate-general and the French National Agency for the Safety of Medicines and Health Products (ANSM) to increase information.

> "'Even if not all the evidence is available, information about risks from drugs should be given sooner rather than later as a precaution.'"

Dominique Martin, director-general of ANSM, recognises that patients should have been warned about the dangers years earlier. "Even if not all the evidence is available, information about risks from drugs should be given sooner rather than later as a precaution. This is the position I defend at the agency", he told *The Lancet*.

Martin acknowledges that the French authorities missed an opportunity to remedy the valproate issue in 2003, would be acceptable. Most doctors told their patients about the risks of valproate, but a certain number didn't, and even 5 years ago some still kept silent as they believed the cause of the problems remained uncertain and that the epilepsy itself rather than the drugs was to blame for malformations and developmental disorders."

"This is a very serious case of negligence", said Irène Frachon, the pulmonologist who 9 years ago broke the scandal of Mediator, an antidiabetes drug that was widely prescribed as an appetite suppressant and lead to up to 2000 deaths from valvular heart disease. "France has learned nothing from the Distilbène scandal, and finds it very difficult to recognise victims of medical accidents or malpractice, and compensate them for the prejudice they have suffered." Distilbène, a synthetic oestrogen prescribed to prevent miscarriages in women with difficult pregnancies, was withdrawn in France in 1977, long after other countries withdrew the drug and long after it had been shown to cause genital anomalies and increase the risk of cancer in female offspring.

France is not the only country to step up warnings about the risks

Valproate de sodium et tératogénicité: quelle chronologie?

1982

Robert E, Giubaud P (1982): Maternal valproic acid and congenital neural tube defects. Lancet 2:937.

1984

DiLiberti JH, Farndon PA, Dennis NR, Curry CJ The fetal valproate syndrome Am J Med Genet 1984 Nov;19(3):473-81

Epicanthus

Saillie métopique

Lèvre supérieure fine

Racine du nez large

Moore et al. 2000

American Journal of Medical Genetics 19:473–481 (1984)

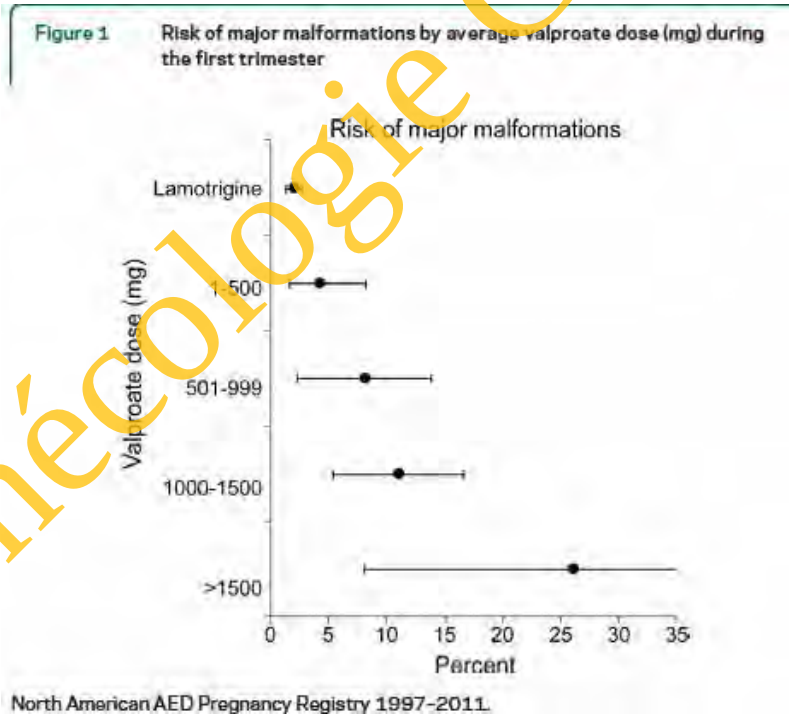
The Fetal Valproate Syndrome

John H. DiLiberti, Peter A. Farndon, Nicholas R. Dennis, and Cynthia J.R. Curry

Departments of Pediatrics and Medical Genetics, Emanuel Hospital, Department of Pediatrics, Oregon Health Sciences University, Portland, and Genetic Services Program, Idaho Department of Health and Welfare, Boise (J.H.D.); University of Southampton, Department of Child Health, Southampton General Hospital, Southampton, U.K. (N.R.D.); Medical Genetics Department, St. Mary's Hospital, Manchester, U.K. (P.A.F.); Department of Medical Genetics, Valley Children's Hospital, Fresno, California (C.J.R.C.)

We evaluated seven children who had been exposed to sodium valproate (or valproic acid) in utero. A consistent facial phenotype was observed in all seven in addition to other birth defects in four. The facial changes consisted of epicanthal folds which continued inferiorly and laterally to form a crease or groove just under the orbit, flat nasal bridge, small upturned nose, long upper lip with a relatively shallow philtrum, a thin upper vermillion border, and downturned angles of the mouth. Hypospadias, strabismus, and psychomotor delay were found in two males; two children had nystagmus and two had low birth weight.

1996-1999 Registres de grossesse



2011

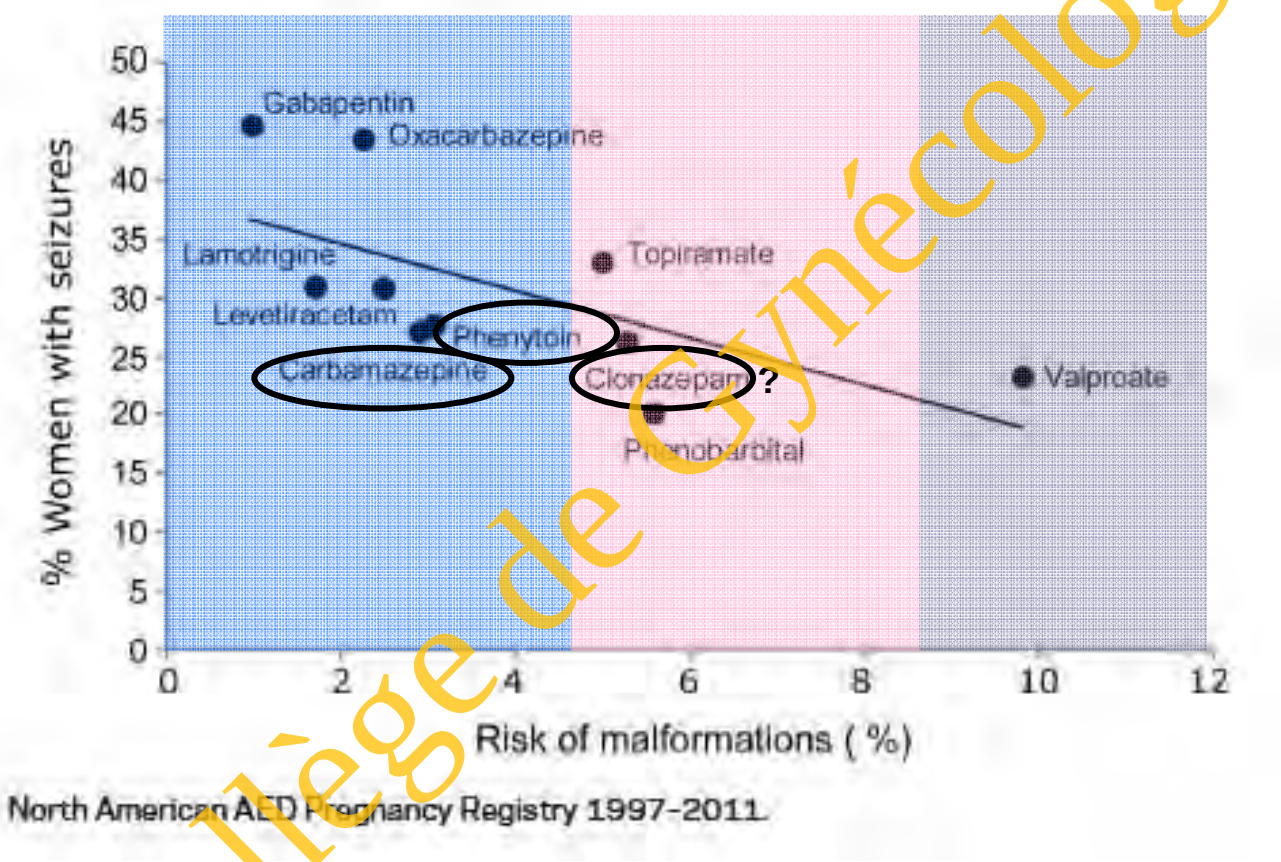
2015

Table 3. Frequencies of major congenital malformations (95% CI) with monotherapy with valproate, carbamazepine, and lamotrigine at different dose levels in EURAP, UKIre, and NAAPR

	EURAP[4]			UKIre[8]			NAAPR[7]		
Drug	Dose range (mg/day)	No. exposed	MCM % (95% CI)	Dose range (mg/day)	Number of exposed	MCM % (95% CI)	Dose range (mg/day)	Number of exposed	MCM % (95% CI)
Valproate	<700	431	5.6 (3.6–8.2)	<600	476	5.0 (3.4–7.4)	1–500	NA	4.3 (0.2–8.3)
	≥700 <1,500	480	10.4 (7.8–13.5)	>600 to <1,000	426	6.1 (4.2–8.8)	501–999	NA	6.8 (1.6–12.1)
	≥1,500	99	24.2 (16.2–33.9)	>1,000	297	10.4 (7.4–14.4)	1,000–1,500	NA	10.7 (5.2–16.1)
							>1,500	NA	26.1 (8.1–44.0)

Epilepsia, 56(7):1006-1019, 2015

Registre Nord Américain
4,899 grossesses en monothérapie vs 442 CTRL



LTG 1562

CBZ 1033

LEV 450

PHT 416

TPM 359

VPA 323

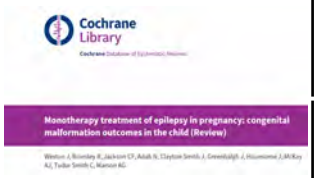
OXCBZ 182

GBP 145

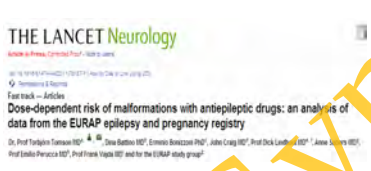
ZNS 90

CNZ 64

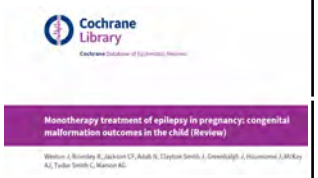
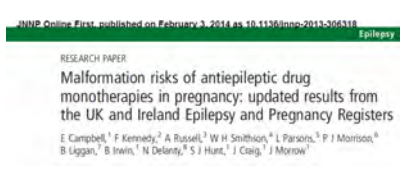
Lamotrigine (Lamictal-LTG-)

MAE	**Cochrane 2016**	**EURAP 2011**		**Registre USA 2012**	**Registre UK 2014**		
							
		n=4540		n=4899	n=3607		
	Taux corrigé pour variance	Taux de MCM à 1 an après naissance		Taux de MCM à 3 mois après naissance	Taux de MCM à 6 semaines naissance		
LTG (mg)	**Toute dose**	<300	≥300	**Toute dose**	<200	200-400	>400
	2,31%	**2%**	**4,5 %**	**2%**	**2,1%**	**2,4%**	**3,4%**
Cas exposés	*4195*	*836*	*444*	*1519*	*1143*	*665*	*267*

Levetiracetam (Keppra-LEV-)

MAE	Cochrane 2016	EURAP 2011	Registre USA 2012	Registre UK 2014
				
		n=4540	n=4899	n=3607
	Taux corrigé pour variance	Taux de MCM à 1 an après naissance	Taux de MCM à 3 mois après naissance	Taux de MCM à 6 semaines naissance
LEV	**Toute dose**	Non communiqué	**Toute dose**	**Toute dose**
	1,77%		**2,4%**	**0%**
Cas exposés	*817*		*447*	*26*

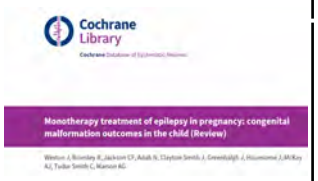
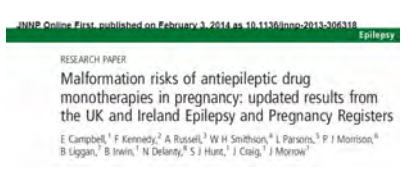
Carbamazépine (Tegretol-CBZ-)

MAE	**Cochrane 2016**	**EURAP 2011**			**Registre USA 2012**	**Registre UK 2014**		
								
		n=4540			n=4899	n=3607		
	Taux corrigé pour variance	Taux de MCM à 1 an après naissance			Taux de MCM à 3 mois après naissance	Taux de MCM à 6 semaines naissance		
CBZ (mg)	**Toute dose**	<400	≥400-<1000	≥1000	**Toute dose**	<500	500-1000	>1000
	4,93%	**3,4%**	**5,3%**	**8,7%**	**3%**	**1,9%**	**2,7%**	**5,3%**
Cas exposés	*4666*	*148*	*1047*	*207*	*1002*	*721*	*739*	*170*

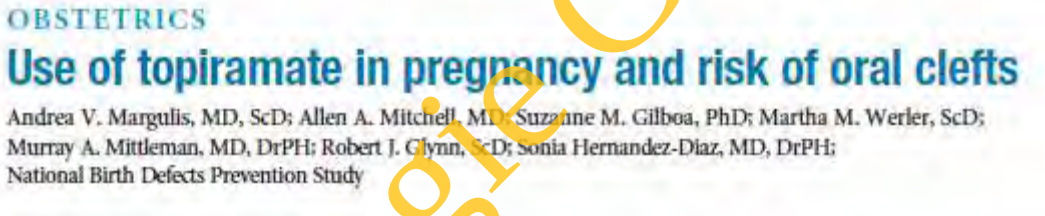
Oxcarbazépine (Trileptal-OXCBZ-) & Gabapentine (Neurontin-GBP-)

MAE	**Cochrane 2016**	**EURAP 2011**	**Registre USA 2012**	**Registre UK 2014**
				
		n=4540	n=4899	n=3607
	Taux corrigé pour variance	Taux de MCM à 1 an après naissance	Taux de MCM à 3 mois après naissance	Taux de MCM à 6 semaines naissance
OXCBZ	**Toute dose**	Non communiqué	**Toute dose**	Non communiqué
	2,39%		**2,2%**	
Cas exposés	*238*		*178*	
GBP	**Toute dose**	Non communiqué	**Toute dose**	**Toute dose**
	1,47%		**0,7%**	**3,2%**
Cas exposés	*190*		*141*	*30*

Phénobarbital (Gardénal-PB-) & Phénytoïne (Dihydan-PHT-)

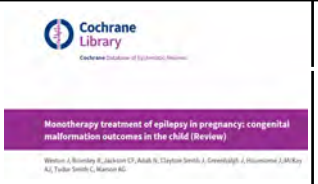
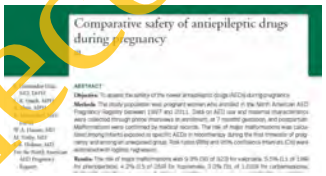
MAE	**Cochrane 2016**	**EURAP 2011**		**Registre USA 2012**	**Registre UK 2014**
					
		n=4540		n=4899	n=3607
	Taux corrigé pour variance	Taux de MCM à 1 an après naissance		Taux de MCM à 3 mois après naissance	Taux de MCM à 6 semaines naissance
PB (mg)	**Toute dose**	<150	≥ 150	**Toute dose**	Non communiqué
	7,1%	**5,4%**	**13 ,7%**	**5,5%**	
Cas exposés	*709*	*157*	*44*	*189*	
PHT	**Toute dose**	Non communiqué		**Toute dose**	**Toute dose**
	6,26%			**2,9%**	**3,7%**
Cas exposés	*1279*			*401*	*78*

Topiramate (Epitomax-TPM-)


OBSTETRICS

Use of topiramate in pregnancy and risk of oral clefts

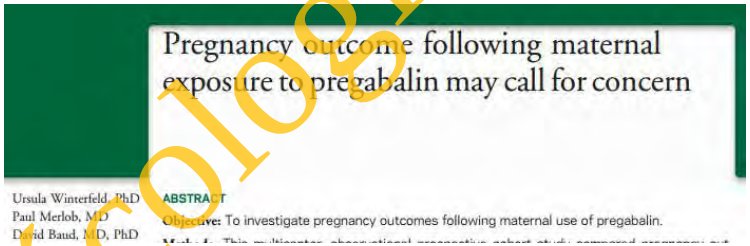
Andrea V. Margulis, MD, ScD; Allen A. Mitchell, MD; Suzanne M. Gilboa, PhD; Martha M. Werler, ScD; Murray A. Mittleman, MD, DrPH; Robert J. Glynn, ScD; Sonia Hernandez-Diaz, MD, DrPH; National Birth Defects Prevention Study

MAE	Cochrane 2016	EURAP 2011	Registre USA 2012	Registre UK 2014
	 Cochrane Library. Monotherapy treatment of epilepsy in pregnancy: congenital malformation outcomes in the child (Review)	 THE LANCET Neurology. Dose-dependent risk of malformations with antiepileptic drugs: an analysis of data from the EURAP epilepsy and pregnancy registry	 Comparative safety of antiepileptic drugs during pregnancy	 JNNP Online First, published on February 3, 2014 as 10.1136/jnnp-2013-306318. Epilepsy. RESEARCH PAPER. Malformation risks of antiepileptic drug monotherapies in pregnancy: updated results from the UK and Ireland Epilepsy and Pregnancy Registers
		n=4540	n=4899	n=3607
	Taux corrigé pour variance	Taux de MCM à 1 an après naissance	Taux de MCM à 3 mois après naissance	Taux de MCM à 6 semaines naissance
TPM	**Toute dose**	Non communiqué	**Toute dose**	**Toute dose**
	4,28%		**4,2%**	**7,1%**
Cas exposés	*473*		*342*	*26*

En bref

Pregabaline (Lyrica)

N= 125, Taux malformation: 6.4%


Pregnancy outcome following maternal exposure to pregabalin may call for concern

Ursula Winterfeld, PhD
Paul Merlob, MD
David Baud, MD, PhD

ABSTRACT

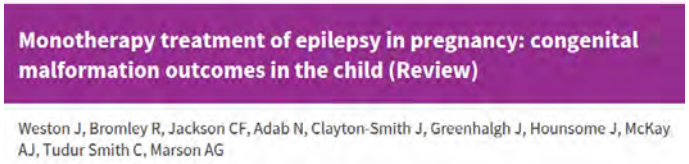
Objective: To investigate pregnancy outcomes following maternal use of pregabalin.

Cochrane Library

Cochrane Database of Systematic Reviews

Zonisamide (Zonegran)

N= 90, Taux malformation: 0%


Monotherapy treatment of epilepsy in pregnancy: congenital malformation outcomes in the child (Review)

Weston J, Bromley R, Jackson CF, Adab N, Clayton-Smith J, Greenhalgh J, Hounsome J, McKay AJ, Tudur Smith C, Marson AG

Lacosamide (Vimpat), Perampanel (Fycompa), Eslicarbazépine (Zebinix) ????

Risques médicamenteux | **tératogénicité** | cognition | comportement | autres

Therapeutic Advances in Neurological Disorders — Review

Management of epilepsy during pregnancy: an update

Sima J. Patel and Page B. Pennell

AED	NAAPR	UK Epilepsy and Pregnancy Register	EURAP
	n = 4899	*n* = 3607	*n* = 4540
	Hernandez-Diaz *et al.* [2012]	Morrow *et al.* [2006]	Tomson *et al.* [2011]
	MCM 3 months after birth	**MCM 6 weeks after birth**	**MCM 12 months after birth**
	% (95% CI) (n)	**% (95% CI) (n)**	**% (95% CI) (n); dose**
Valproic acid	9.3% (6.4–13.0) (30)	6.2% (4.6–8.2) (44)	5.6% (3.60–8.17) (24); <700 mg/day 10.4% (7.83–13.50) (50); ⩾700 mg/day to <1500 mg/day 24.2% (16.19–33.89) (24); ⩾1500 mg/day
Topiramate	4.2% (2.4–6.8) (15)	7.1% (2.0–22.6) (2)	–
Oxcarbazepine	2.2% (0.6–5.5) (4)	–	–
Gabapentin	0.7% (0.02–3.8) (1)	3.2% (0.6–16.2) (1)	–
Zonisamide	0% (0.0–3.3) (0)	–	–
Clonazepam	3.1% (0.4–10.8) (2)	–	–
Phenobarbital	5.5% (2.8–9.7) (11)	–	5.4% (2.51–10.04) (9); <150 mg/day 13.7% (5.70–26.26) (7); ⩾150 mg/day
Lamotrigine	2% (1.4–2.8) (31)	3.2% (2.1–4.9) (21)	2.0% (1.19–3.24) (17); <300 mg /day 4.5% (2.77–6.87) (20); ⩾300 mg/day
Levetiracetam	2.4% (1.2–4.3) (11)	0% (0.0–14.9) (0)	–
Carbamazepine	3% (2.1–4.2) (31)	2.2% (1.4–3.4) (20)	3.4% (1.11–7.71) (5); <400 mg/day 5.3% (4.07–6.89) (56); ⩾400 mg/day to <1000 mg/day 8.7% (5.24–13.39) (18); ⩾1000
Lacosamide			
Perampanel			

Suivi renforcé +++ si ATCD de malformation

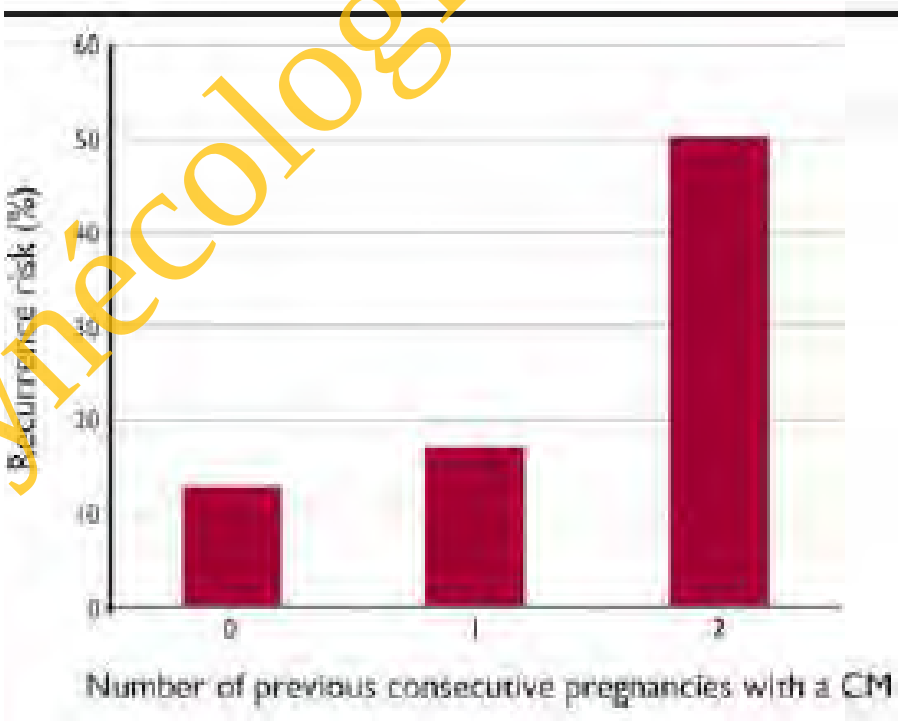
Epilepsia, 54(1):165–171, 2013
doi: 10.1111/epi.12001

FULL-LENGTH ORIGINAL RESEARCH

Recurrence risk of congenital malformations in infants exposed to antiepileptic drugs in utero

*Ellen Campbell, *Emma Devenney, *Jim Morrow, †Aline Russell, ‡William Henry Smithson, §Linda Parsons, ¶Iain Robertson, *Beth Irwin, #Patrick J. Morrison, *Stephen Hunt, and *John Craig

*Neurology Department, Belfast Health and Social Care Trust, Royal Victoria Hospital, Belfast, United Kingdom; †Department of Clinical Neurophysiology, Institute of Neurological Sciences, Southern General Hospital, Glasgow, United Kingdom; ‡Academic Unit of Primary Medical Care, Samuel Fox House, University of Sheffield, Northern General Hospital, Sheffield, United Kingdom; §Neurology Department, Luton & Dunstable Hospitals NHS Trust, Luton, United Kingdom; ¶Department of Obstetrics and Gynaecology, Sharoe Green Unit, Royal Preston Hospital, Preston, United Kingdom; and #Department of Medical Genetics, Belfast Health and Social Care Trust, Belfast City Hospital, Belfast, United Kingdom



Risque de 50% si malformation congénitale lors des 2 premières grossesses

Prédisposition génétique??

Le cas du Valproate de sodium

FORMULAIRE D'ACCORD DE SOINS
TRAITEMENT DES PATIENTES PAR VALPROATE

Document à remplir et à signer

L'objectif de l'accord de soins est de garantir que les patientes qui sont en âge ou vont être en âge d'être enceintes (en âge de procréer) soient pleinement informées et comprennent les risques de malformations congénitales et de troubles neurodéveloppementaux chez les enfants nés de femmes ayant pris du valproate pendant la grossesse.

Cet accord de soins doit être complété par le médecin spécialiste et par chaque patiente, avant le début de l'instauration de son traitement par valproate et à chaque réévaluation de celui-ci (au minimum lors de chaque prescription annuelle).

Il doit être présenté à la pharmacie pour toute délivrance du médicament.

Informations sur la patiente

Nom : _____ Prénom : _____

Si patiente mineure et/ou protégée par la loi, nom de son représentant* _____

A CONFIRMATION PAR LE MÉDECIN PRESCRIPTEUR

- Je confirme que la patiente susnommée présente une réponse insuffisante ou une intolérance aux autres traitements et que le valproate est la seule option thérapeutique. ☐

J'ai discuté des points suivants avec la patiente susnommée/son représentant* :

- Les enfants nés de mères exposées au valproate pendant la grossesse, présentent un risque élevé de malformations congénitales (environ 10 %) et un large éventail de troubles neurodéveloppementaux dont des troubles du spectre autistique (jusqu'à 30 % à 40 %) susceptibles d'entraîner des troubles importants de l'apprentissage. ☐
- La nécessité d'utiliser la dose minimale efficace. ☐
- La nécessité d'une contraception efficace (si la patiente est en âge de procréer). ☐
- La nécessité de réévaluer régulièrement le traitement, au moins une fois par an, et si la patiente envisage une grossesse. ☐
- La nécessité de consulter en urgence si la patiente est enceinte ou pense l'être pendant le traitement. ☐
- J'ai remis un exemplaire de la brochure d'information patient à la patiente elle-même/son représentant.* ☐

Nom du prescripteur : _____ Date : _____

Signature et tampon : _____

B POUR LA PATIENTE/SON REPRÉSENTANT

Veuillez lire attentivement ce qui suit et cocher la case correspondante pour confirmer votre accord.

Je soussigné(e) _____ comprends :

- Que le traitement par valproate m'est prescrit car je présente une réponse insuffisante ou une intolérance aux autres traitements et que le valproate est la seule option thérapeutique. ☐
- Que les enfants nés de mères exposées au valproate pendant la grossesse présentent un risque élevé de malformations congénitales (environ 10 %) et de nombreux types de troubles neurodéveloppementaux dont des troubles du spectre autistique (jusqu'à 30 % à 40 %). ☐
- Que si je suis en âge de procréer, je dois utiliser une contraception efficace. ☐
- Que je n'envisage pas de grossesse. ☐
- Que mon traitement sera réévalué régulièrement et au moins une fois par an. ☐
- Que je dois demander une consultation AVANT d'envisager de concevoir un enfant. ☐
- Qu'en cas de grossesse ou si je pense être enceinte pendant le traitement par valproate, je dois consulter immédiatement mon médecin. ☐

Nom de la patiente/représentant* : _____ Date : _____

World Report

France steps up warning measures for valproate drugs

Last week, France attempted to correct its past mishandling of concerns about sodium valproate drugs for epilepsy in pregnancy with a raft of new steps. Barbara Casassus reports from Paris.

French Health Minister Marisol Touraine has issued a new series of measures to help ensure that no more women of childbearing age take sodium valproate drugs without being fully aware of the potential dangers to their unborn babies.

The move came after a report from the general inspectorate for social affairs (IGAS) last month criticised the authorities and lead drug company Sanofi for not reacting more rapidly when congenital malformations and then development disorders started to be linked to Sanofi's Dépakine, three valproate derivatives, and generic drugs that are prescribed to prevent epilepsy and bipolar seizures.

The drug, which was launched in France in 1967, has probably caused malformations in about 450 children born between 2006 and 2014, according to IGAS. The first scientific indications of the problem appeared in 1982, whereas those for neurodevelopmental difficulties emerged much later, from 2000. Formal proof of the latter was established in 2011, and now it is estimated that 40% of the children exposed to valproate had a 10-point lower than average IQ at the age of linked to valproate and other drugs from the local register in the Rhône-Alpes region in southern France, and create a legal expert mission to determine compensation for victims based on the lack of information and damages caused. All this comes on top of earlier steps taken by the ministry's health directorate-general and the French National Agency for the Safety of Medicines and Health Products (ANSM) to increase information.

> "'Even if not all the evidence is available, information about risks from drugs should be given sooner rather than later as a precaution.'"

Dominique Martin, director-general of ANSM, recognises that patients should have been warned about the dangers years earlier. "Even if not all the evidence is available, information about risks from drugs should be given sooner rather than later as a precaution. This is the position I defend at the agency", he told *The Lancet*.

Martin acknowledges that the French authorities missed an opportunity to remedy the valproate issue in 2003, would be acceptable. Most doctors told their patients about the risks of valproate, but a certain number didn't, and even 5 years ago some still kept silent as they believed the cause of the problems remained uncertain and that the epilepsy itself rather than the drugs was to blame for malformations and developmental disorders."

"This is a very serious case of negligence", said Irène Frachon, the pulmonologist who 9 years ago broke the scandal of Mediator, an antidiabetes drug that was widely prescribed as an appetite suppressant and lead to up to 2000 deaths from valvular heart disease. "France has learned nothing from the Distilbène scandal, and finds it very difficult to recognise victims of medical accidents or malpractice, and compensate them for the prejudice they have suffered." Distilbène, a synthetic oestrogen prescribed to prevent miscarriages in women with difficult pregnancies, was withdrawn in France in 1977, long after other countries withdrew the drug and long after it had been shown to cause genital anomalies and increase the risk of cancer in female offspring.

France is not the only country to step up warnings about the risks

Valproate de sodium et troubles neurodéveloppementaux : quelle chronologie?

2000 Moore SJ, Turnpenny P, Quinn A, et al. A clinical study of 57 children with fetal anticonvulsant syndromes. *J Med Genet*. 2000;37(7):489-497.

2004 Adab N, Kini U, Vinten J, Ayres J, Baker G , Clayton-Smith J, Coyle H, Fryer A, Gorry J, Gregg J, Mawer G, Nicolaides P, Pickering L, Tunnicliffe L, Chadwick D W The longer term outcome of children born to mothers with epilepsy J Neurol Neurosurg Psychiatry 2004;75:1575–1583

2009 Meador KJ, Baker GA, Browning N, Clayton-Smith J, Combs-Cantrell DT, Cohen M, Kalayjian MA, Kanner A, Liporace JD, Pennell PB, Privitera M, Loring DW, for the NEAD Study Group* Cognitive Function at 3 Years of Age after Fetal Exposure to Antiepileptic Drugs N Engl J Med 2009;360:1597-605

2013 Meador KJ, Baker GA, Browning N, Cohen MJ, Bromley RL, Clayton-Smith J, Kalayjian LA, Kanner A, Liporace JD, Pennell PB, Privitera M, Loring DW for the NEAD Study GroupFetal antiepileptic drug exposure and cognitive outcomes at age 6 years (NEAD study): a prospective observational study Lancet Neurol. 2013 March ; 12(3): 244–252

2015 Baker GA, Bromley RL, Briggs M, Cheyne CP, Cohen MJ, García-Fiñana M, Gummery A, Kneen R, Loring, DW, Mawer G, Meador KJ, Shallcross R, Clayton-Smith J, On behalf of the Liverpool and Manchester Neurodevelopment Group IQ at 6 years after in utero exposure to antiepileptic drugs A controlled cohort study *Neurology*. 2015;84: 390

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 APRIL 16, 2009 VOL. 360 NO. 16

Cognitive Function at 3 Years of Age after Fetal Exposure to Antiepileptic Drugs

Les doses médianes de carbamazepine étaient de 750 mg/j, de 433 mg/j pour la lamotrigine, de 398 mg/j pour la phénytoïne, et de 1000 mg/l pour le valproate

Table 2. IQ Scores of Children at 3 Years of Age According to In Utero Exposure to Antiepileptic Drugs.*

Variable	Carbamazepine (N=73)	Lamotrigine (N=84)	Phenytoin (N=48)	Valproate (N=53)
Mean IQ (95% CI)†	98 (95–102)	101 (98–104)	99 (94–104)	92 (88–97)
Mean difference in IQ from valproate group (95% CI)‡	6 (0.6–12.0)	9 (3.1–14.6)	7 (0.2–14.0)	
P value§	0.04	0.009	0.04	

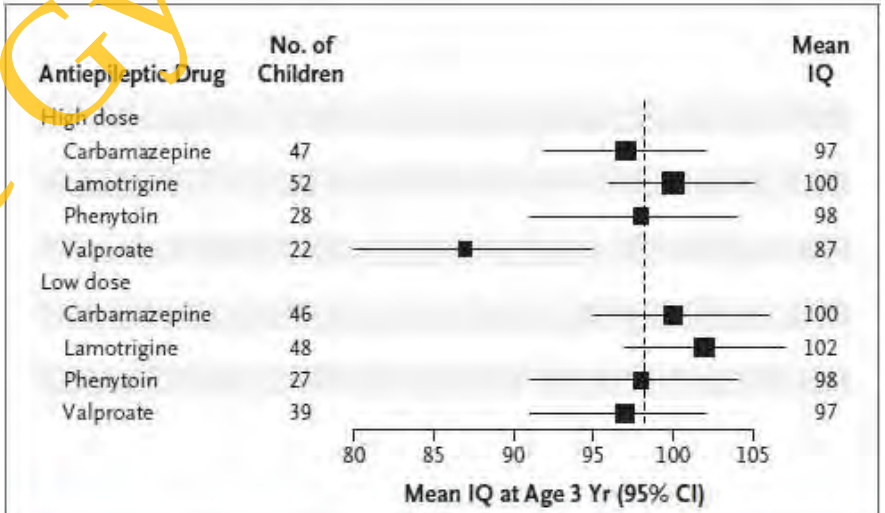


Figure 1. IQ Scores of Children Who Were Exposed to Antiepileptic Drugs In Utero, According to Drug and Dose.

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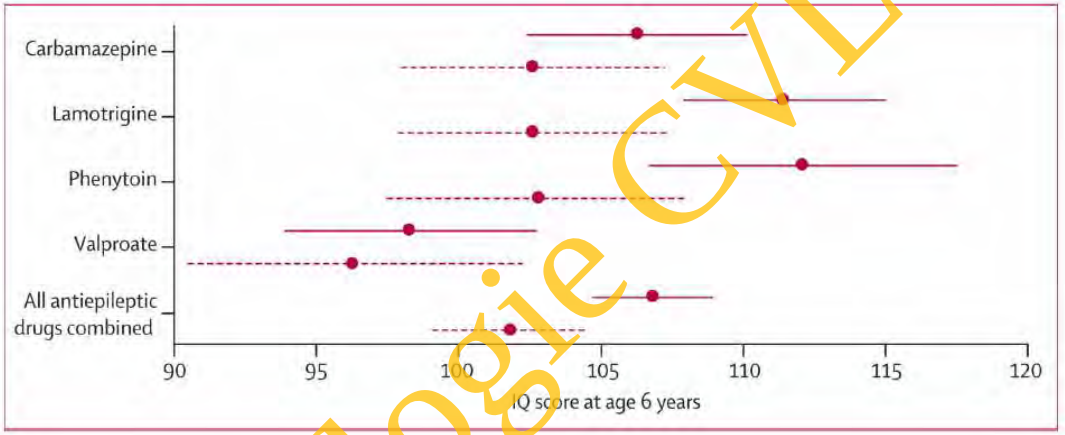
Author Manuscript

Published in final edited form as:
Lancet Neurol. 2013 March ; 12(3): 244–252. doi:10.1016/S1474-4422(12)70323-X.

Fetal antiepileptic drug exposure and cognitive outcomes at age 6 years (NEAD study): a prospective observational study

Kimford J Meador, Gus A Baker, Nancy Browning, Morris J Cohen, Rebecca L Bromley, Jill Clayton-Smith, Laura A Kalayjian, Andres Kanner, Joyce D Liporace, Page B Pennell, Michael Privitera, and David W Loring* for the NEAD Study Group

224 enfants suivis sur 6 ans

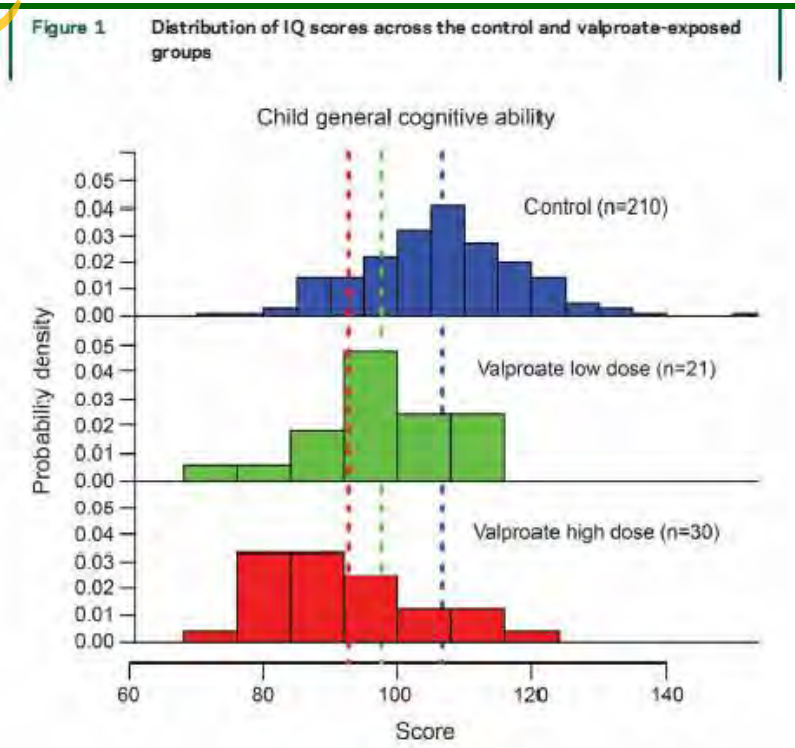


QI moyen sous VPA: 97 vs 105 (CBZ) ou 108 (LTG)
Corrélation négative entre hautes doses de valproate et QI

IQ at 6 years after in utero exposure to antiepileptic drugs

A controlled cohort study *Neurology*. 2015;84: 390

QI global plus bas en moyenne de 9.7 points chez enfants exposés à VPA> 800 mg/j



Vanoverloop D, Schnell R, Harvey E, Holmes L. 1992. The effects of prenatal exposure to phenytoin and other anticonvulsants on intellectual function at 4 to 8 years of age. Neurotoxicol Teratol; 14:329-335.

Reinisch J, Sanders S, Mortensen E, Rubin D. 1995. In utero exposure to phenobarbital and intelligence deficits in adult men. JAMA; 274:1518-1525.

QI affecté par prise de Phénobarbital, Phénytoïne ou la polythérapie

Table 3
Mental and Motor Development Quotient

	MeDQ			MoDQ		
	mean	95% CI	p	mean	95% CI	p
AED usage						
No AED (32)	92.3	81.4–103.2		94.7	84.9–104.5	
AED used	88.6	85.5–91.6	.087[c]	90	87.3–92.8	.002[c]
Monotherapy (246)	90.6	86.9–94.3	.79	93.1	89.7–96.5	.172
PB (41)	90.3	83.6–97.0		94.6	87.0–102.2	
PHT (29)	90.3	77.3–103.3		100	91.6–108.4	
CBZ (101)	93.1	87.7–98.5		95	89.7–100.3	
VPA (71)	86.9	79.1–94.7	.08[d]	86.1	79.3–92.9	0.031[d]
Others (4)	84.6	44.2–125.0		96.4	73.8–119.0	
Polytherapy (122)[a]	83.8	78.3–89.3	.160[e]	83	78.4–87.6	.012[e]
Two AEDs (97)	82.9	76.3–89.5		84.3	78.8–89.8	
PB + PHT (25)	83.9	70.3–97.5		84.1	75.3–92.9	
PB + CBZ (20)	76.6	65.3–87.9		87.6	75.8–99.4	
CBZ + PHT (3)	97.2	75.5–118.9		106	20.8–191.4	
VPA + CBZ (9)	78.2	43.4–113.0		89.5	72.7–106.3	
VPA + LTG (5)	81	7.4–154.6		64.9	21.7–108.1	
VPA + PB (3)	84.1	24.9–143.3		78.3	40.3–116.3	
VPA + PHT (3)	61.4	17.9–104.9		75.6	19.6–131.6	
VPA + CLZ (3)	58.5	0.0–123.4		68.4	0.0–158.6	
Three AEDs (20)	94.4	85.4–103.4		83.9	76.3–91.5	
Four AEDs (5)	76.2	63.9–88.5		68.1	52.1–84.1	

ELSEVIER
Available online at www.sciencedirect.com
ScienceDirect
Epilepsy & Behavior 12 (2008) 229–236
Epilepsy & Behavior
www.elsevier.com/locate/yebeh

Motor and mental development of infants exposed to antiepileptic drugs in utero

Risques médicamenteux	tératogénicité	**cognition**	comportement	autres

Table 2. IQ Scores of Children at 3 Years of Age According to In Utero Exposure to Antiepileptic Drugs.*

Variable	Carbamazepine (N=73)	Lamotrigine (N=84)	Phenytoin (N=48)	Valproate (N=53)
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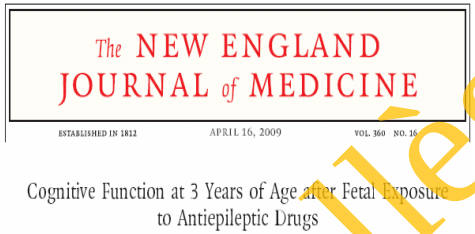
P value§	0.04	0.009	0.04	

QI non affecté par la prise de Lamotrigine



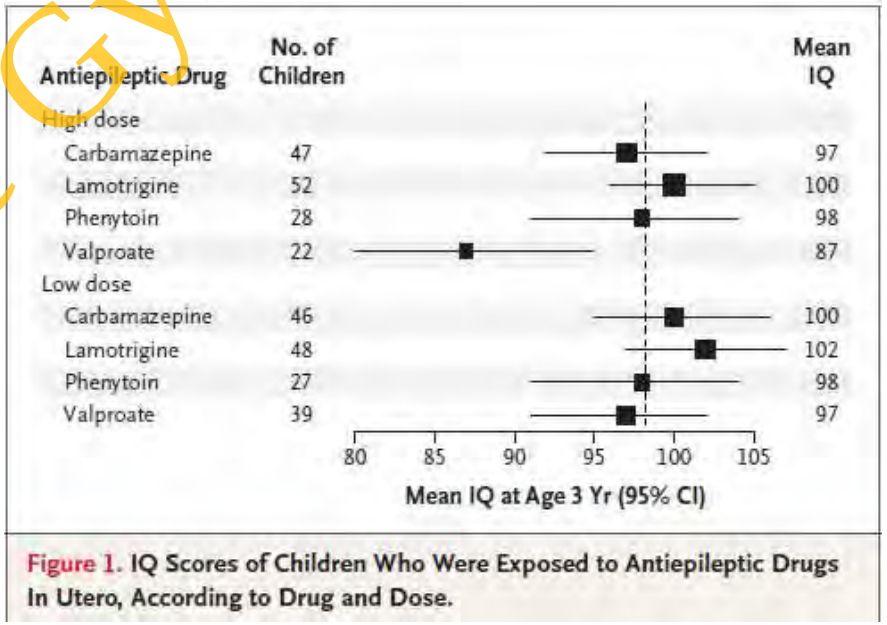


Figure 1. IQ Scores of Children Who Were Exposed to Antiepileptic Drugs In Utero, According to Drug and Dose.

Risques médicamenteux	tératogénicité	**cognition**	comportement	autres

QI a priori non affecté par la prise de Carbamazépine

Normal intelligence in children with prenatal exposure to carbamazepine

E. Gaily, MD; E. Kantola-Sorsa, MA; V. Hiilesmaa, MD; M. Isoaho, MA; R. Matila, MD; M. Kotila, MD; T. Nylund, MD; A. Bardy, MD; E. Kaaja, MSc; and M.-L. Granström, MD

IQ score group	Number of children	Verbal mean ± SEM	Nonverbal mean ± SEM	Full scale mean ± SEM
Study group all	182	92.8 ± 1.3	100.3 ± 1.2	96.0 ± 1.2
No drug exposure	45	94.3 ± 2.6	98.6 ± 2.9	95.6 ± 2.8
Monotherapy exposure	107	94.4 ± 1.7	101.9 ± 1.4	98.0 ± 1.6
CBZ monotherapy	86	96.2 ± 1.9	103.1 ± 1.5	99.7 ± 1.8
VPA monotherapy	13	83.5 ± 3.8	96.3 ± 4.8	89.7 ± 3.6
Other monotherapy†	8	91.1 ± 6.4	96.9 ± 4.6	93.6 ± 5.0
Polytherapy exposure‡	30	84.9 ± 2.5*	97.1 ± 2.9	89.5 ± 2.4
VPA combinations	17	81.5 ± 2.8	96.1 ± 3.7	86.6 ± 2.4
Control group all	141	94.9 ± 1.2	102.4 ± 1.2	97.6 ± 1.4

Arch Dis Child. 2011 Jul;96(7):643-7. Epub 2011 Mar 17.

Neurodevelopment of children exposed in utero to lamotrigine, sodium valproate and carbamazepine.

Cummings C, Stewart M, Stevenson M, Morrow J, Nelson J.

Bradbury Centre, 1-17 Lisburn Road, Belfast BT9 7AA, UK; cliona.cummings@belfasttrust.hscni.net.

Mais…….

Abstract

Objective To establish the relative risks of in utero exposure to lamotrigine (LTG), sodium valproate (NaV) and carbamazepine (CBZ) monotherapy for neurodevelopment. Design Observational cohort study. Patients and methods The study group consisted of children in Northern Ireland aged 9-60 months born to mothers who had enrolled with the UK Epilepsy and Pregnancy Register. The control group consisted of children identified from the Child Health System database across Northern Ireland. Data were gathered on covariates recognised as influencing child development. Main outcome measures Neurodevelopment assessed using either the Bayley Scales of Infant Development or the Griffiths Mental Development Scales. Results 210 children underwent assessment by a single researcher blinded to antiepileptic drug exposure. 23 (39.6%) children exposed in utero to NaV, 10 (20.4%) exposed to CBZ and one (2.9%) exposed to LTG had evidence of mild or significant developmental delay, compared to two (4.5%) children in the control group. Multivariable analysis demonstrated that in utero exposure to NaV (OR 26.1, 95% CI 4.9 to 139; p<0.001) and to CBZ (OR 7.7, 95% CI 1.4 to 43.1; p<0.01) but not to LTG had a significant detrimental effect on neurodevelopment. Conclusion In utero exposure to LTG did not have the detrimental effect on child development that was seen with NaV and with CBZ.

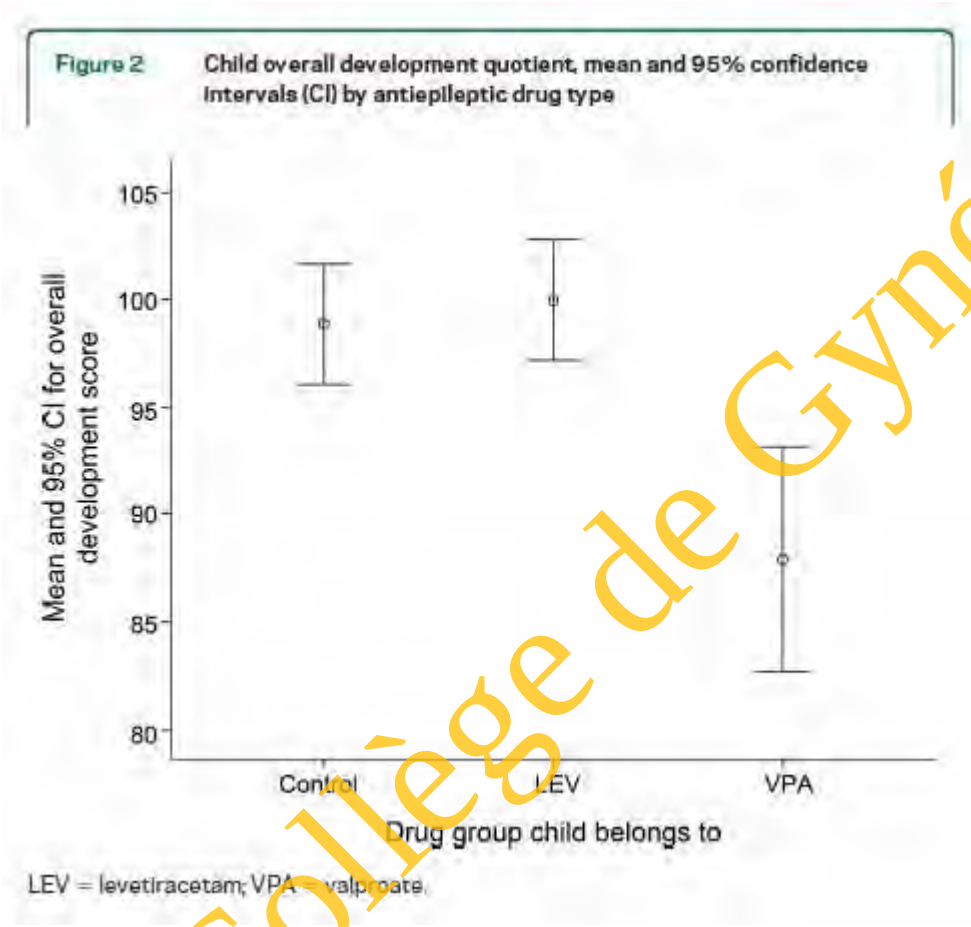
Risques médicamenteux	tératogénicité	**cognition**	comportement	autres

Child development following in utero exposure

Levetiracetam vs sodium valproate

QI non affecté par la prise de Lévétiracétam

Et de Topiramate…..



Cognition in school-age children exposed to levetiracetam, topiramate, or sodium valproate

Rebecca L. Bromley, PhD ABSTRACT

Neurology® 2016;87:1–11

Mais ….prudence

Faibles effectifs dans toutes les études !!

Le cas du Valproate de sodium

FORMULAIRE D'ACCORD DE SOINS
TRAITEMENT DES PATIENTES PAR VALPROATE

Document à remplir et à signer

L'objectif de l'accord de soins est de garantir que les patientes qui sont en âge ou vont être en âge d'être enceintes (en âge de procréer) soient pleinement informées et comprennent les risques de malformations congénitales et de troubles neurodéveloppementaux chez les enfants nés de femmes ayant pris du valproate pendant la grossesse.

Cet accord de soins doit être complété par le médecin spécialiste et par chaque patiente, avant le début de l'instauration de son traitement par valproate et à chaque réévaluation de celui-ci (au minimum lors de chaque prescription annuelle).

Il doit être présenté à la pharmacie pour toute délivrance du médicament.

Informations sur la patiente

Nom : _____ Prénom : _____

Si patiente mineure et/ou protégée par la loi, nom de son représentant* _____

A CONFIRMATION PAR LE MÉDECIN PRESCRIPTEUR

- Je confirme que la patiente susnommée présente une réponse insuffisante ou une intolérance aux autres traitements et que le valproate est la seule option thérapeutique. ☐

J'ai discuté des points suivants avec la patiente susnommée/son représentant* :

- Les enfants nés de mères exposées au valproate pendant la grossesse, présentent un risque élevé de malformations congénitales (environ 10 %) et un large éventail de troubles neurodéveloppementaux dont des troubles du spectre autistique (jusqu'à 30 % à 40 %) susceptibles d'entraîner des troubles importants de l'apprentissage. ☐
- La nécessité d'utiliser la dose minimale efficace. ☐
- La nécessité d'une contraception efficace (si la patiente est en âge de procréer). ☐
- La nécessité de réévaluer régulièrement le traitement, au moins une fois par an, et si la patiente envisage une grossesse. ☐
- La nécessité de consulter en urgence si la patiente est enceinte ou pense l'être pendant le traitement. ☐
- J'ai remis un exemplaire de la brochure d'information patient à la patiente elle-même/son représentant.* ☐

Nom du prescripteur : _____ Date : _____

Signature et tampon : _____

B POUR LA PATIENTE/SON REPRÉSENTANT

Veuillez lire attentivement ce qui suit et cocher la case correspondante pour confirmer votre accord.

Je soussigné(e) _____ comprends :

- Que le traitement par valproate m'est prescrit car je présente une réponse insuffisante ou une intolérance aux autres traitements et que le valproate est la seule option thérapeutique. ☐
- Que les enfants nés de mères exposées au valproate pendant la grossesse présentent un risque élevé de malformations congénitales (environ 10 %) et de nombreux types de troubles neurodéveloppementaux dont des troubles du spectre autistique (jusqu'à 30 % à 40 %). ☐
- Que si je suis en âge de procréer, je dois utiliser une contraception efficace. ☐
- Que je n'envisage pas de grossesse. ☐
- Que mon traitement sera réévalué régulièrement et au moins une fois par an. ☐
- Que je dois demander une consultation AVANT d'envisager de concevoir un enfant. ☐
- Qu'en cas de grossesse ou si je pense être enceinte pendant le traitement par valproate, je dois consulter immédiatement mon médecin. ☐

Nom de la patiente/représentant* : _____ Date : _____

World Report

France steps up warning measures for valproate drugs

Last week, France attempted to correct its past mishandling of concerns about sodium valproate drugs for epilepsy in pregnancy with a raft of new steps. Barbara Casassus reports from Paris.

French Health Minister Marisol Touraine has issued a new series of measures to help ensure that no more women of childbearing age take sodium valproate drugs without being fully aware of the potential dangers to their unborn babies.

The move came after a report from the general inspectorate for social affairs (IGAS) last month criticised the authorities and lead drug company Sanofi for not reacting more rapidly when congenital malformations and then development disorders started to be linked to Sanofi's Dépakine, three valproate derivatives, and generic drugs that are prescribed to prevent epilepsy and bipolar seizures.

The drug, which was launched in France in 1967, has probably caused malformations in about 450 children born between 2006 and 2014, according to IGAS. The first scientific indications of the problem appeared in 1982, whereas those for neurodevelopmental difficulties emerged much later, from 2000. Formal proof of the latter was established in 2011, and now it is estimated that 40% of the children exposed to valproate had a 10-point lower than average IQ at the age of linked to valproate and other drugs from the local register in the Rhône-Alpes region in southern France, and create a legal expert mission to determine compensation for victims based on the lack of information and damages caused. All this comes on top of earlier steps taken by the ministry's health directorate-general and the French National Agency for the Safety of Medicines and Health Products (ANSM) to increase information.

> "'Even if not all the evidence is available, information about risks from drugs should be given sooner rather than later as a precaution.'"

Dominique Martin, director-general of ANSM, recognises that patients should have been warned about the dangers years earlier. "Even if not all the evidence is available, information about risks from drugs should be given sooner rather than later as a precaution. This is the position I defend at the agency", he told *The Lancet*.

Martin acknowledges that the French authorities missed an opportunity to remedy the valproate issue in 2003, would be acceptable. Most doctors told their patients about the risks of valproate, but a certain number didn't, and even 5 years ago some still kept silent as they believed the cause of the problems remained uncertain and that the epilepsy itself rather than the drugs was to blame for malformations and developmental disorders."

"This is a very serious case of negligence", said Irène Frachon, the pulmonologist who 9 years ago broke the scandal of Mediator, an antidiabetes drug that was widely prescribed as an appetite suppressant and lead to up to 2000 deaths from valvular heart disease. "France has learned nothing from the Distilbène scandal, and finds it very difficult to recognise victims of medical accidents or malpractice, and compensate them for the prejudice they have suffered." Distilbène, a synthetic oestrogen prescribed to prevent miscarriages in women with difficult pregnancies, was withdrawn in France in 1977, long after other countries withdrew the drug and long after it had been shown to cause genital anomalies and increase the risk of cancer in female offspring.

France is not the only country to step up warnings about the risks

Valproate de sodium et troubles autistiques: quelle chronologie?

2000 Moore SJ, Turnpenny P, Quinn A, et al. A clinical study of 57 children with fetal anticonvulsant syndromes. *J Med Genet*. 2000;37(7):489-497.

2005 Rasalam AD, Hailey H,Williams JH, et al. Characteristics of fetal anticonvulsant syndrome associated autistic disorder. *Dev Med Child Neurol*. 2005; 47(8):551-555.

2008 Bromley RL, Mawer G, Clayton-Smith J, Baker GA; Liverpool and Manchester Neurodevelopment Group. Autism spectrum disorders following in utero exposure to antiepileptic drugs. *Neurology*. 2008;71 (23):1923-1924.

2013 **Christensen J, Kopps Grønborg T, Sørensen MJ, Schendel D, Thorlund Parner E, Henning Pedersen L, Vestergaard M Prenatal Valproate Exposure and Risk of Autism Spectrum Disorders and Childhood Autism JAMA, April 24, 2013—Vol 309, No. 16**

2015 Wood AG, Nadebaum C, Anderson V, Reutens D, Barton S, O'Brien TJ, Vajda F Prospective assessment of autism traits in children exposed to antiepileptic drugs during pregnancy Epilepsia, 56(7):1047-1055, 2015

ORIGINAL CONTRIBUTION

Prenatal Valproate Exposure and Risk of Autism Spectrum Disorders and Childhood Autism

Jakob Christensen, PhD
Therese Koops Grønborg, MSc
Merete Juul Sørensen, PhD
Diana Schendel, PhD
Erik Thorlund Parner, PhD
Lars Henning Pedersen, PhD
Mogens Vestergaard, PhD

Importance Valproate is used for the treatment of epilepsy and other neuropsychological disorders and may be the only treatment option for women of childbearing potential. However, prenatal exposure to valproate may increase the risk of autism.

Objective To determine whether prenatal exposure to valproate is associated with an increased risk of autism in offspring.

Design, Setting, and Participants Population-based study of all children born alive in Denmark from 1996 to 2006. National registers were used to identify children exposed to valproate during pregnancy and diagnosed with autism spectrum disorders (childhood autism [autistic disorder], Asperger syndrome, atypical autism, and other

JAMA, April 24, 2013—Vol 309, No. 16

Cohorte de 600 000 enfants (Danemark) nés entre 1996 et 2006

508 nés de mère sous VPA:

- 4.4% troubles spectre autistique (vs 1.5% dans cohorte globale)
- 2.5% autisme (vs 0.5% dans cohorte globale)

FULL-LENGTH ORIGINAL RESEARCH

Prospective assessment of autism traits in children exposed to antiepileptic drugs during pregnancy

*†§Amanda G. Wood, *¶Caroline Nadebaum, *#Vicki Anderson, **David Reutens, *¶Sarah Barton, ††Terence J. O'Brien, and ††‡‡Frank Vajda

Epilepsia, 56(7):1047–1055, 2015
doi: 10.1111/epi.13007

105 enfants Australiens âgés de 6-8 ans

Évaluation avec le Childhood Autism Rating Scale (CARS)

11 enfants avec traits autistiques (10.5%):

-9 sous VPA (2 monothérapies et 7 polythérapies)

-2 sous CBZ (2 monothérapies)

Table 3. Rates of elevated CARS scores

	CARS >30	CARS 27–29	Total
Valproate (monotherapy)	1/26	1/26	2/26
	3.8%	3.8%	7.7%
Valproate (polytherapy)	6/15	1/15	7/15
	40.0%	6.7%	46.7%
Carbamazepine (monotherapy)	1/34	1/34	2/34
	2.9%	2.9%	5.9%
Other (mono/polytherapy)	0/30	0/30	0/30
	0.0%	0.0%	0.0%
Total	8/105	3/105	11/105
	7.6%	2.9%	10.5%

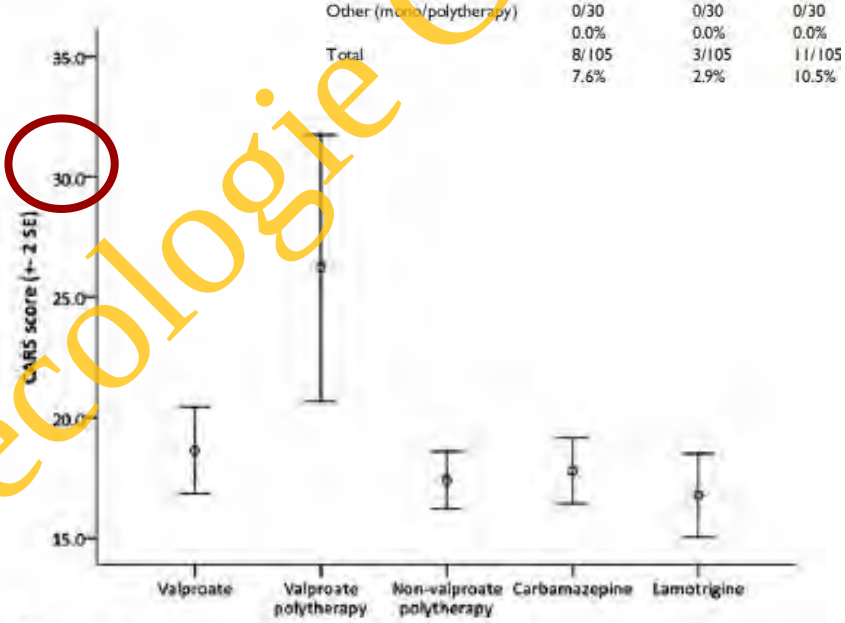


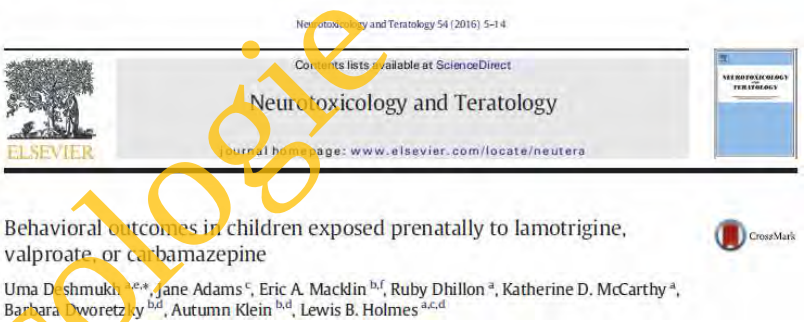
Figure 1.
CARS scores of AED-exposed children.

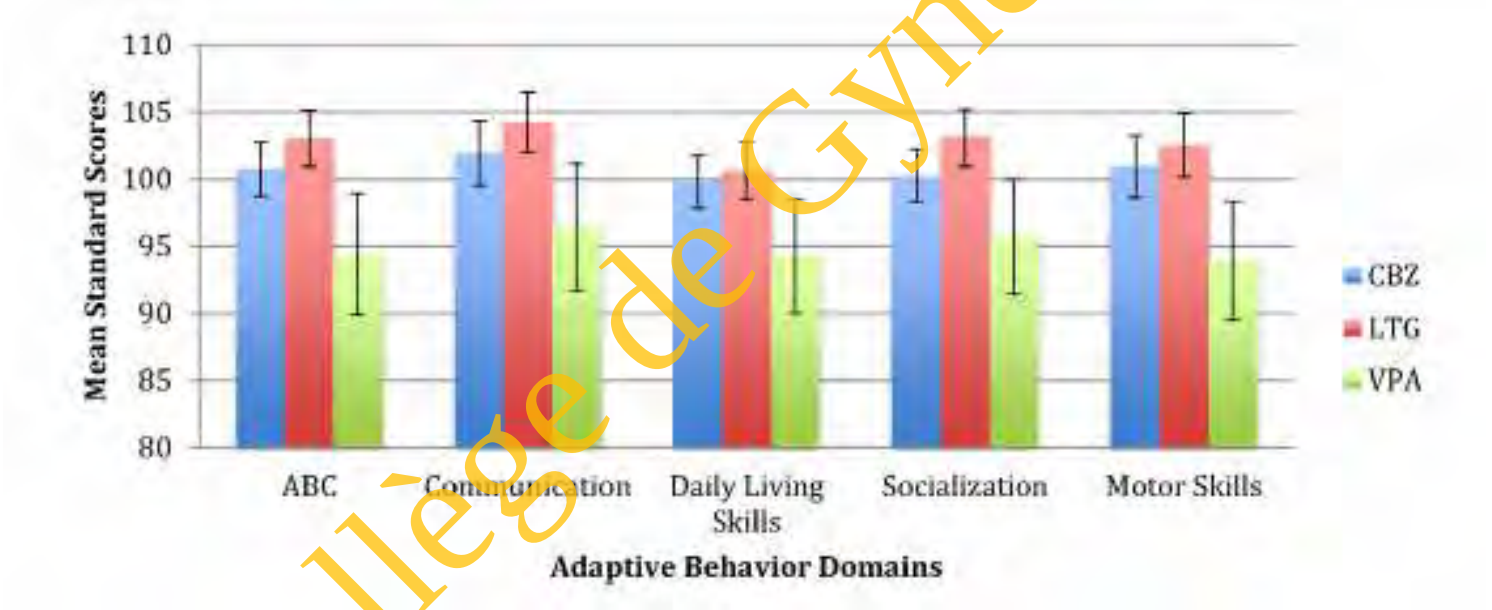
Claire dose-dépendance

Table 5. Predictors of CARS Scores in linear regression

Variable	B coefficient (std. error)	t (p)
Mean valproate dose	0.002 (0.001)	3.20 (0.002)
Folic acid first trimester	−8.631 (2.830)	−3.05 (0.003)
Marijuana use	14.844 (2.88)	5.16 (<0.001)
Mean carbamazepine dose	0.000 (0.001)	−0.07 (0.945)
Polytherapy	1.727 (1.126)	1.53 (0.128)
Seizure(s) during pregnancy	0.963 (1.013)	0.95 (0.345)
Maternal IQ	0.000 (0.044)	0.007 (0.994)
Socioeconomic status	−0.014 (0.027)	−0.52 (0.607)
Constant	25.831 (5.007)	5.16 (<0.001)

Risques	tératogénicité	cognition	**comportement**	autres





LTG=104
CBZ=97
VPA=51

J Neurol (2014) 261:579–588
DOI 10.1007/s00415-013-7239-x

ORIGINAL COMMUNICATION

Fetal growth restriction and birth defects with newer and older antiepileptic drugs during pregnancy

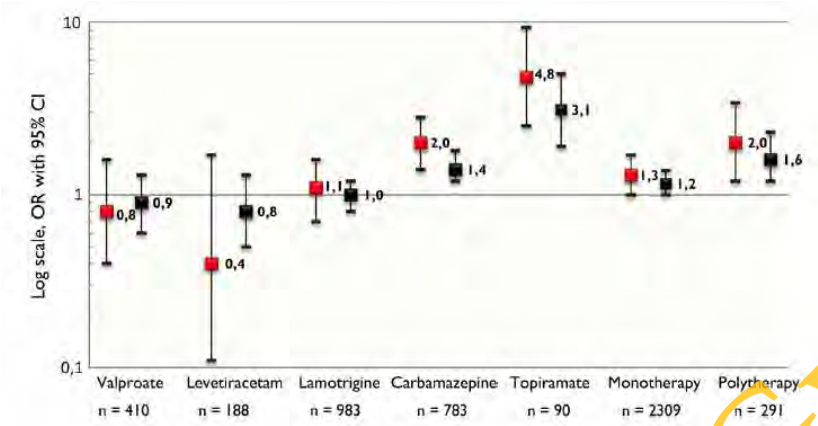
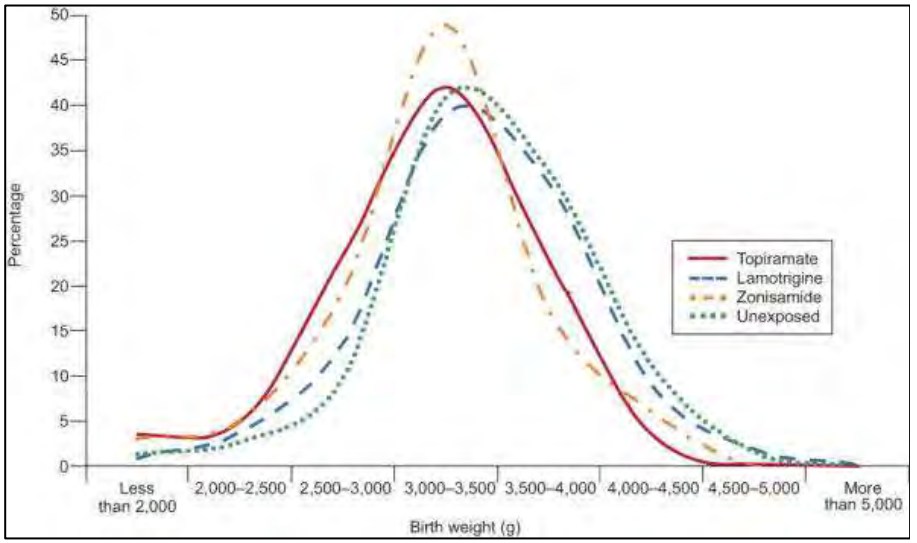


Fig. 1 Fetal growth restriction in children exposed to antiepileptic drugs Compared to the reference group.

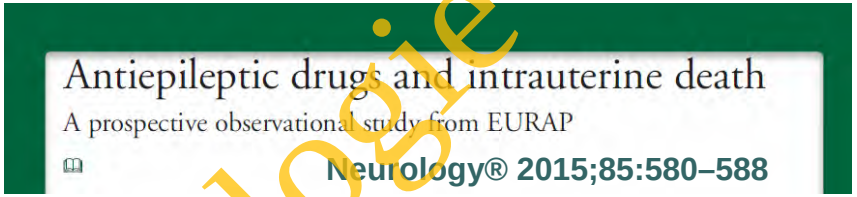
Plus faible poids de naissance avec Topiramate et Zonisamide

Association Between Topiramate and Zonisamide Use During Pregnancy and Low Birth Weight.
Hernandez-Diaz, Sonia; MD, DrPH; Mittendorf, Robert; MD, DrPH; Smith, Caitlin; Hauser, W; Yerby, Mark; Holmes, Lewis

Obstetrics & Gynecology. 123(1):21-28, January 2014.
DOI: 10.1097/AOG.0000000000000018



7,055 grossesses exposées



Monothérapie: lamotrigine (1,910), carbamazepine (1,713), valproic acid (1,171), levetiracetam (324), oxcarbazepine (262), phenobarbital (260)

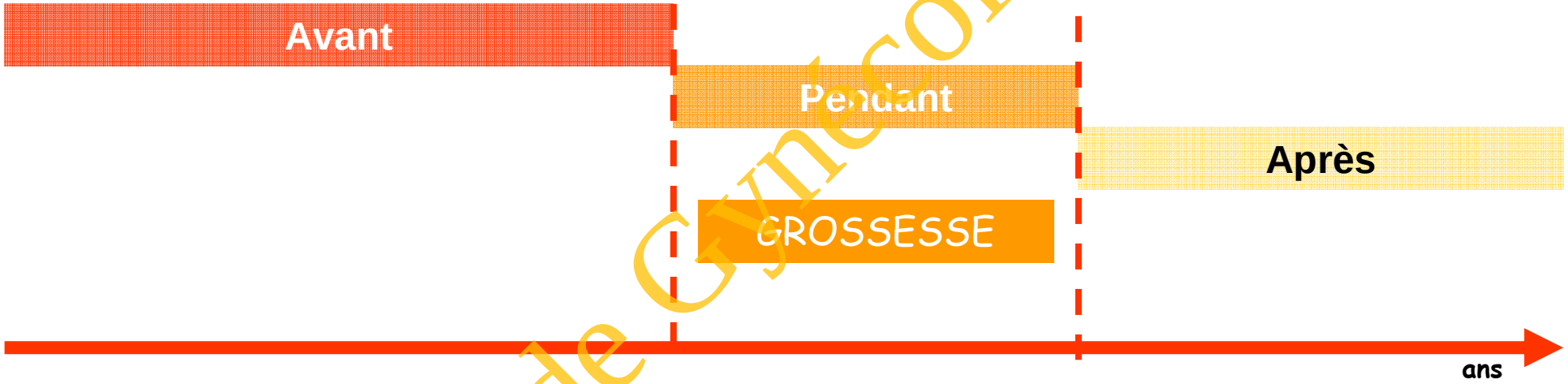
- Polythérapie: 1415

Taux de mort intra-utérine: 8% d'avortements spontanés et 0,005% de morts-nés vs dans population normale (Danemark): 11% et 0,3%

Pas d'impact monothérapie, type MAE ou dose MAE en monothérapie

FDR +++:
Polythérapie
ATCD de malformation congénitale chez l'un des parents

Gestion grossesse	avant	pendant	après



Maîtrise grossesse: contraception

Planification/Information grossesse

Gestion MAE

Gestion épilepsie

Coordination

Suivi renforcé

Rééquilibration MAE

Allaitement

Suivi devenir enfants

Gestion grossesse	**avant**	pendant	après

Conseils préconceptionnels

1. Programmation très en amont de la grossesse:
   a. Réévaluer nécessité du traitement
   b. Simplifier, arrêter ou changer le traitement
2. Information éclairée du couple
3. Concertation avec gynécologue
4. Gestion période préconceptionnelle :
   a. Folates
   b. Vitamine K: au nouveau-né

Gestion grossesse	**avant**	pendant	après

Folates en préventif: discuté
donné en principe de précaution 0.4 mg/j ou 5mg/j?

Table 2. Major congenital malformations in entire evaluable cohort.

MCM group	Number of MCMs in PCFA group (n=1,935)	%, 95% C.I.	Number of MCMs in no PCFA group (n=2,375)	%, 95% C.I.
All	76	3.9 (3.1 – 4.9)	53	2.2 (1.0 – 3.3)
NTD	8	0.4 (0.2 – 0.8)	8	0.3 (0.2 – 0.7)
Oral Clefts	8	0.4 (0.2 – 0.8)	11	0.5 (0.3 – 0.8)
Hypospadias	11	0.6 (0.3 – 1.0)	6	0.3 (0.1 – 0.6)
Cardiac	19	1.0 (0.6 – 1.5)	11	0.5 (0.3 – 0.8)

PCFA = pre-conceptual folic acid; NTD = neural tube defect; MCM = major congenital malformation.

JNNP Online First, published on October 31, 2008 as 10.1136/jnnp.2008.156109

Folic acid use and major congenital malformations in offspring of women with epilepsy. A prospective study from the UK Epilepsy and Pregnancy Register.

James I Morrow, Stephen J Hunt, Aline J Russell, W Henry Smithson, Linda Parsons, Iain Robertson, Ruth Waddell, Beth Irwin, Patrick J Morrison, John J Craig

DOI: 10.1111/j.1471-0528.2007.01552.x
www.blackwellpublishing.com/bjog

Epidemiology

Antiepileptic drug use, folic acid supplementation, and congenital abnormalities: a population-based case–control study

D Kjær,[a] E Horvath-Puhó,[b] J Christensen,[c] M Vestergaard,[d] AE Czeizel,[e] HT Sørensen,[f] J Olsen[g]

J Neurol
DOI 10.1007/s00415-008-0029-1

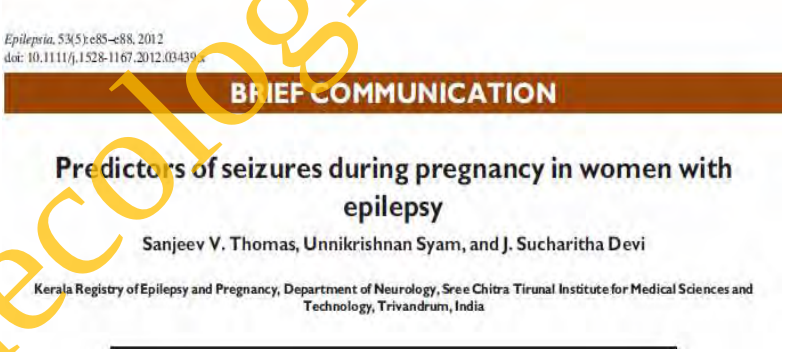
ORIGINAL COMMUNICATION

Spontaneous abortion and the prophylactic effect of folic acid supplementation in epileptic women undergoing antiepileptic therapy

Sabine Pittschieler
Christoph Brezinka
Beate Jahn
Eugen Trinka
Iris Unterberger
Judith Dobesberger
Gerald Walser
Andrea Auckenthaler
Norbert Embacher
Gerhard Bauer
Gerhard Luef

Evolution épilepsie pendant grossesse

On multiple logistic regression, prepregnancy seizure was the most important predictor of seizures during pregnancy


Epilepsia, 53(5):e85–e88, 2012
doi: 10.1111/j.1528-1167.2012.03439.x

BRIEF COMMUNICATION

Predictors of seizures during pregnancy in women with epilepsy

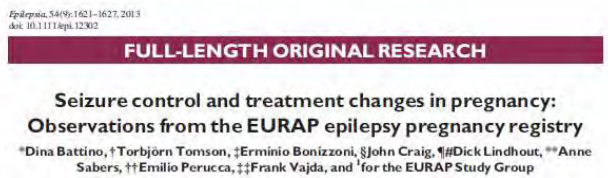
Sanjeev V. Thomas, Unnikrishnan Syam, and J. Sucharitha Devi

Kerala Registry of Epilepsy and Pregnancy, Department of Neurology, Sree Chitra Tirunal Institute for Medical Sciences and Technology, Trivandrum, India

3,806 grossesses de 3,451 femmes épileptiques:

Risque identique de crises sur toute la grossesse

3,5% de crises lors de l'accouchement


Epilepsia, 54(9):1621–1627, 2013
doi: 10.1111/epi.12302

FULL-LENGTH ORIGINAL RESEARCH

Seizure control and treatment changes in pregnancy: Observations from the EURAP epilepsy pregnancy registry

*Dina Battino, †Torbjörn Tomson, ‡Erminio Bonizzoni, §John Craig, ¶#Dick Lindhout, **Anne Sabers, ††Emilio Perucca, ‡‡Frank Vajda, and for the EURAP Study Group

Gestion grossesse	avant	**pendant**	après

Gérer un éventuel déséquilibre de l'épilepsie

- Recours temporaire à l'adjonction de benzodiazépines
- Majoration de doses après le premier trimestre
- Adjonction tardive 2ème médicament si besoin

Monitoring plasmatique des MAE

Table 2
Changes in the serum concentrations of new antiepileptic drugs during pregnancy.

	Reduction in serum concentration
Lamotrigine	50–60%
Levetiracetam	40–60%
Oxcarbazepine	30–40%
Eslicarbazepine	n.a.
Topiramate	30–40%
Gabapentin	n.a.
Pregabalin	n.a.
Zonisamide	20–40%
Lacosamide	n.a.
Retgabine/ezogabine	n.a.
Stiripentol	n.a.
Perampanel	n.a.

n.a. = no data available.

Gestion grossesse	avant	**pendant**	après

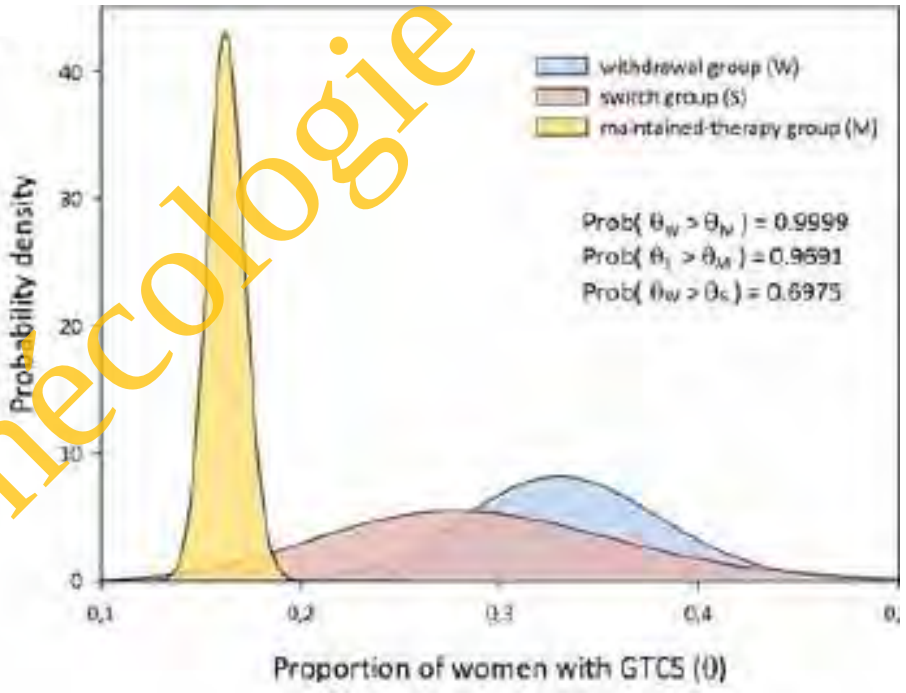
BRIEF COMMUNICATION

Withdrawal of valproic acid treatment during pregnancy and seizure outcome: Observations from EURAP

*[1]Torbjörn Tomson, †[1]Dina Battino, ‡[1]Erminio Bonizzoni, §John Craig, ¶**Dick Lindhout, ††‡‡Emilio Perucca, §§Anne Sabers, ¶¶Sanjeev V Thomas, ***Frank Vajda, and [2]for the EURAP Study Group

Epilepsia, 57(8):e173–e177, 2016
doi: 10.1111/epi.13437

Arrêter le Valproate si grossesse non programmée?



Risque de faire des CGTC doublé dans groupes où VPA est arrêté ou remplacé

Table 1. Demographic data and seizure control

	VPA withdrawn without any switch during first trimester (*n* = 93)		VPA switched to other AED during first trimester (*n* = 38)		VPA maintained during the first trimester (*n* = 1,588)[a]	
Three most common concomitant AEDs	Lamotrigine, carbamazepine, levetiracetam		Phenobarbital, lamotrigine, clonazepam		Lamotrigine, carbamazepine, phenobarbital	
	Mean	Range	Mean	Range	Mean	Range

Gestion grossesse	avant	**pendant**	après

BRIEF COMMUNICATION

SUDEP and epilepsy-related mortality in pregnancy

*Stephan Edey, †‡Nicholas Moran, and ‡Lina Nashef

Epilepsia, 55(7):e72–e74, 2014
doi: 10.1111/epi.12621

Arrêter le Valproate si grossesse non programmée?

Table 1. The maternity, maternity mortality, and epilepsy-related mortality figures for the trienniums between and including 1991–2008 (adapted from CMACE[2])

Triennium period	No. of maternities	No. of maternal deaths	No. of deaths due to epilepsy	Proportion of epilepsy-related deaths	Rate of epilepsy-related deaths per 100,000 maternities
1991–1993	2,315,204	228	9	0.04	0.39
1994–1996	2,197,640	268	19	0.07	0.86
1997–1999	2,123,614	242	9	0.04	0.42
2000–2002	1,997,472	261	13	0.05	0.65
2003–2005	2,114,004	295	11	0.04	0.52
2006–2008	2,291,463	261	14	0.05	0.61

7 SUDEP (74%)

9 sous Lamotrigine (64%)

J Neurol (2013) 260:484–488
DOI 10.1007/s00415-012-6662-8

ORIGINAL COMMUNICATION

Generalized tonic–clonic seizures and antiepileptic drugs during pregnancy—a matter of importance for the baby?

Markus Rauchenzauner · Margit Ehrensberger · Manuela Prieschl · Klaus Kapelari · Melanie Bergmann · Gerald Walser · Sabrina Neururer · Iris Unterberger · Gerhard Luef

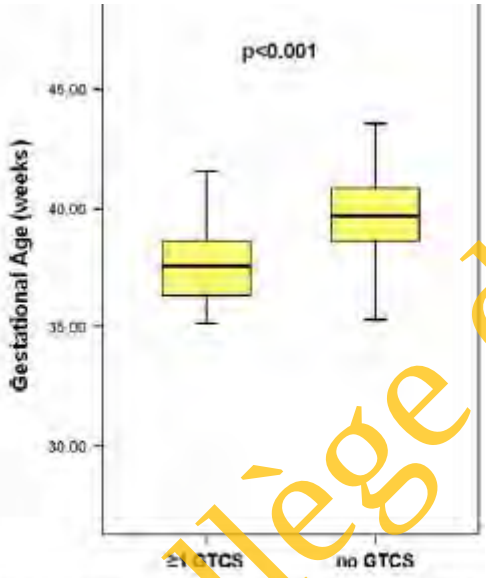


Fig. 1 Gestational age in WWE with ≥1 GTCS vs. no GTCS

Table 2 Neonatal outcome and GTCS

	≥1 GTCS ($n = 14$)	No GTCS ($n = 115$)	P value
Maternal age (years)	28.0 (17.0–42.0)	29.0 (15.0–40.0)	>0.05
Primiparous	8 (57.1)	69 (60.0)	>0.05
Smoker	3 (21.4)	15 (13.0)	>0.05
GA (weeks)	37.5 (35.1–41.6)	39.7 (29.4–46.3)	≤0.001
Pre-term	4 (28.6)	8 (7.0)	0.042
Term	10 (71.4)	102 (88.7)	0.042
Post-term	0 (0.0)	5 (4.3)	0.042
LBW	3 (21.4)	8 (7.0)	>0.05
SGA^{W}	1 (7.1)	4 (3.5)	>0.05
$SGA^{W/L}$	1 (7.1)	12 (10.4)	>0.05
SGA^{L}	0 (0.0)	10 (8.7)	>0.05

Values are median (range) or absolute numbers (percentage); GTCS generalized tonic–clonic seizures

GA gestational age, SGA^{W} small for gestational age regarding weight, $SGA^{W/L}$ SGA regarding weight and/or length, SGA^{L} SGA regarding length, *BW* birthweight, *LBW* low birthweight

Effet des crises sur la grossesse

Prématurité

Plus petit poids de naissance

Gestion grossesse	avant	**pendant**	après

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Obstetric outcome in women with epilepsy: a hospital-based, retrospective study

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Monitoring obstétrical: grossesse à risque?

Prééclampsie sévère: OR, 5,0 (1.3-19.9) ?

Saignement précoce: OR, 2,3 (1.2-4.3)

Table 3. Pregnancy and delivery outcome in 104 women with epilepsy using antiepileptic drugs as monotherapy or polytherapy compared with a control group

Outcome	No epilepsy (reference) (*n* = 205)	Epilepsy with lamotrigine (*n* = 30)		Epilepsy with carbamazepine (*n* = 28)		Epilepsy with valproate (*n* = 19)		Epilepsy with polytherapy (*n* = 27)	
	% (*n*)	% (*n*)	Unadj. OR (95% CI)	% (*n*)	Unadj. OR (95% CI)	% (*n*)	Unadj. OR (95% CI)	% (*n*)	Unadj. OR (95% CI)
Pre-edampsia									
All	5.4 (11)	20.0 (6)	4.4 (1.5–13.0)	7.1 (2)	1.4 (0.3–6.5)	10.5 (2)	2.1 (0.4–10.1)	11.1 (3)	2.2 (0.6–8.5)
Severe	1.5 (3)	10.0 (3)	7.5 (1.4–39.0)	8.0 (2)	5.2 (0.8–32.5)	5.3 (1)	3.7 (0.4–37.8)	7.4 (2)	5.4 (0.9–33.8)
Vaginal bleeding									
<12 weeks	3.9 (8)	20.0 (6)	6.2 (2.0–19.3)	14.3 (4)	4.1 (1.1–14.7)	15.8 (3)	4.6 (1.1–19.1)	25.9 (7)	8.6 (2.8–26.3)
Induction caesarean section	11.2 (23)	36.7 (11)	4.6 (1.9–10.8)	10.7 (3)	1.0 (0.3–3.4)	26.3 (5)	2.8 (0.9–8.6)	25.9 (7)	2.8 (1.1–7.3)
All	12.7 (26)	40.0 (12)	4.6 (2.0–10.6)	25.0 (7)	2.3 (0.9–5.9)	42.1 (8)	5.0 (1.8–13.6)	29.6 (8)	2.9 (1.2–7.3)
Acute	8.3 (17)	26.7 (8)	4.0 (1.6–10.4)	14.3 (4)	1.8 (0.6–5.9)	31.6 (6)	5.1 (1.7–15.1)	14.8 (4)	1.9 (0.6–6.2)
Postpartum haemorrhage	20.5 (42)	25.0 (8)	1.4 (0.6–3.4)	21.4 (6)	1.1 (0.4–2.8)	47.4 (9)	3.5 (1.3–9.1)	36.0 (9)	1.6 (0.7–4.0)
Major congenital malformation	1.0 (2)	10.0 (3)	11.3 (1.8–70.6)	8.0 (2)	7.8 (1.1–57.8)	5.3 (1)	5.6 (0.5–65.2)	7.4 (2)	8.1 (1.1–60.2)

Y-a-t-il des préconisations particulières pour l'accouchement ?

Non:

Pas d'indication de principe à un accouchement déclenché ou à une césarienne

Péridurale recommandée +++

Non:

Rassurer ++ obstétriciens et anesthésistes

Concertation d'amont +++

Gestion grossesse	avant	pendant	après

Dépister +++ la dépression du postpartum

FULL-LENGTH ORIGINAL RESEARCH

Depression and anxiety in women with epilepsy during pregnancy and after delivery: A prospective population-based cohort study on frequency, risk factors, medication, and prognosis

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Les femmes épileptiques, surtout traitées, sont plus à risque de dépression et d'anxiété pendant et après +++ la grossesse

Importance +++ du dépistage pendant et en post partum

Gestion grossesse	avant	pendant	après

Allaitement

Une femme épileptique peut-elle allaiter ?

Oui

Psychiatry and Clinical Neurosciences 2010; 64: 460–468 doi:10.1111/j.1440-1819.2010.02126.x

Review Article

Is breast-feeding of infants advisable for epileptic mothers taking antiepileptic drugs?

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Non

1. Effet bénéfique de l'allaitement:

Nutritionnel/Immunologique

Développemental/Psychologique

2. Eviction syndrome de sevrage
3. Pas plus de toxicité que passage transplacentaire
4. Études montrant effet bénéfique sur cognition

1. Effets secondaires accumulation MAE chez nouveau-né
2. Principe de précaution

Adjusted IQs at Age 6 Years Across Antiepileptic Drugs (AEDs) Comparing Breastfed vs Nonbreastfed Children[a]

	IQ, Mean (95% CI)			
AED Group	Breastfed	Nonbreastfed	Difference	*P* Value
All AEDs	108 (105 to 111) (n = 78)	104 (101 to 106) (n = 103)	4 (0 to 8)	.04
Carbamazepine	107 (101 to 113) (n = 23)	105 (99 to 110) (n = 24)	2 (−6 to 11)	.61
Lamotrigine	113 (110 to 117) (n = 27)	110 (107 to 113) (n = 34)	3 (2 to 8)	.23
Phenytoin	104 (99 to 110) (n = 17)	108 (103 to 113) (n = 20)	−4 (−12 to 4)	.23
Valproate	106 (97 to 115) (n = 11)	94 (88 to 100) (n = 25)	12 (1 to 24)	.04

Merci à tous!

Avant

Pendant

Après

GROSSESSE

ANS

Maîtrise grossesse: contraception

Planification/Information grossesse

Gestion MAE

Gestion épilepsie

Coordination

Suivi renforcé

Rééquilibration MAE

Allaitement

Suivi devenir enfants