

Supplementary files

Title: Gabapentin and Pregabalin Use in First Trimester of Pregnancy and Risk of Specific Congenital Anomalies: an IMI ConcePTION European case-malformed control study

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Supplementary table 1. Data sources contributing to the study

Centre	Years	Births covered	Number of CA registrants
EUROmediCAT registries			
Belgium, Antwerp	01/01/1997-31/12/2019	446,639	12,171
Croatia, Zagreb	01/01/1995-31/12/2017	142,525	2,669
Denmark, Odense	01/01/1995-31/12/2020	133,692	3,733
France, Paris	01/01/2001-31/12/2020	518,539	16,803
France, La Reunion	01/01/2005-31/12/2020	228,378	7,195
Germany, Saxony-Anhalt	01/01/2000-31/12/2020	364,845	11,372
Ireland, Cork and Kerry	01/01/1996-31/12/2020	221,342	6,179
Italy, Emilia Romagna	01/01/2008-31/12/2020	481,627	12,925
Italy, Tuscany	01/01/1995-31/12/2020	708,533	15,742
Malta	01/01/1996-31/12/2020	107,029	3,467
Netherlands, Northern	01/01/1995-31/12/2020	463,453	13,249
Poland, excluding Wielkopolska	01/01/1999-31/12/2020	6,840,733	108,700
Poland, Wielkopolska	01/01/1999-31/12/2020	818,311	21,162
Spain, Valencian region	01/01/2013-31/12/2019	263,321	7,800
Switzerland, Vaud	01/01/1997-31/12/2020	189,005	7,039
Healthcare database			
France, EFEMERIS	01/01/2004-31/12/2020	145,303	3,940
Total	01/01/1995-31/12/2020	12,073,275	254,146

Supplementary table 2. List of medications used for exclusion of registrants with maternal use of known major teratogens during first trimester of pregnancy (n = 569 registrants)

Medication class	Medication	ATC code
Valproic acid	valproic acid	N03AG01
	valpromide	N03AG02
Retinoids	retinoids for treatment of psoriasis	D05BB
	retinoids for treatment of acne	D10BA
	alitretinoin	D11AH04
Immunosuppressants	mycophenolic acid	L04AA06
	thalidomide	L04AX02
	methotrexate low dose	L04AX03
Oral anticoagulants and Vitamin K antagonist	anticoagulants	B01AA
Antimitotics	antimitotic	L01A
		L01B
		L01C

Supplementary table 3. List of ICD-10 codes of the congenital anomalies analysed in the study

Congenital anomalies subgroup	ICD-10 codes
Congenital heart defects	Q20-Q26
Ventricular septal defect	Q210
Severe congenital heart defects	Q200, Q201, Q203, Q204, Q212, Q213, Q220, Q224, Q225, Q226, Q230, Q232, Q233, Q234, Q251, Q252, Q262
Limb anomalies	Q65-Q74
Urinary anomalies	Q60-Q64, Q794
Genital anomalies	Q50-Q52, Q54-Q56
Hypospadias	Q54

Supplementary Table 4. Number of congenital anomalies, number of exposed, and odds ratio (OR) for gabapentinoids exposure in EUROCAT non-genetic congenital anomaly subgroups.

Congenital anomaly subgroup of interest	Cases of interest		Controls							
	Total of cases	Exposed cases n (%)	Total of controls ^{a,b}	Exposed controls n (%)	crude OR (95% CI)	Adj OR ^c (95% CI)	Total of controls ^a	Exposed controls n (%)	Crude OR (95% CI)	Adj OR ^c (95% CI)
Congenital heart defects	52244	15 (0.03)	93989	16 (0.02)	1.69 (0.83 - 3.43)	1.61 (0.78 – 3.30)	23893	6 (0.02)	1.14 (0.46 – 3.21)	1.38 (0.53 – 4.10)
Ventricular septal defect	28483	12 (0.04)	93989	16 (0.02)	2.48 (1.15 – 5.21)	2.46 (1.12 – 5.28)	23893	6 (0.02)	1.68 (0.65 – 4.82)	2.26 (0.81 – 6.91)
Severe congenital heart defects	11846	4 (0.03)	93989	16 (0.02)	2.16 (0.76 - 6.14) ^d	2.28 (0.80 – 6.50) ^d	23893	6 (0.02)	1.40 (0.42 – 4.65) ^d	1.83 (0.52 – 6.47) ^d
Limb anomalies	25497	4 (0.02)	120736	27 (0.02)	0.77 (0.29 – 2.10) ^d	1.07 (0.39 - 2.93) ^d	23893	6 (0.02)	0.65 (0.19 – 2.16) ^d	0.76 (0.21 - 2.83) ^d
Urinary anomalies	22294	4 (0.02)	123939	27 (0.02)	0.91 (0.34 – 2.46) ^d	0.71 (0.26 – 1.94) ^d	23893	6 (0.02)	0.74 (0.22 – 2.47) ^d	0.83 (0.23 -3.03) ^d
Genital anomalies	15120	4 (0.03)	131113	27 (0.02)	1.42 (0.52 – 3.84) ^d	1.52 (0.56 – 4.12) ^d	23893	6 (0.02)	1.09 (0.33 – 3.64) ^d	1.22 (0.35 – 4.24) ^d
Hypospadias ^e	12793	3 (0.02)	71776	16 (0.02)	1.19 (0.38 – 3.77) ^d	1.38 (0.43 – 4.42) ^d	14769	NR	-	-

Footnote: **OR:** odds ratio; **NR:** not reported due to data privacy, cells with less than 3 were not shared; ^aComplete cases; ^bNo of controls used in each analysis varied according to exclusion of case group and congenital anomaly subgroup at hierarchical level above where relevant; ^cAdjusted for registry, calendar year and maternal age;

^dFirth bias correction; ^eOnly among male registrants

Supplementary Table 5. Description of the congenital anomalies, infant/fetus and maternal characteristics of the 37 registrants exposed to gabapentin and pregabalin.

No	Exposed to	Description of congenital anomalies					Infant/fetus characteristics		Maternal characteristics	
		ICD code	ICD 10 description	Additional data from free text record	Classification of anomaly	Age at diagnosis	Year of birth		Maternal disease	Co-medications during the first trimester of pregnancy
R1	Gabapentin	Q7781	Other osteochondrodysplasia with defects of growth of tubular bones and spine	Multiple epiphyseal dysplasia	Genetic syndrome, skeletal dysplasia and monogenic disorder (control genetic)	Over 12 months	2000-2004	Multiple birth	Multiple epiphyseal dysplasia	Levonorgestrel and ethinylestradiol, carbamazepine, BCG vaccine, paracetamol
								Gestational length: 37-41 weeks		
								Low birth weight: no		
								Karyotype: COMP mutation		
R2	Gabapentin	Q220	Pulmonary valve atresia	Open septum pulmonary atresia	Multiple congenital anomalies	Prenatal diagnosis	2005-2009	Singleton	Other congenital malformations of uterus and cervix, facial neuralgia	Carbamazepine, dextropropoxyphene
								Gestational length: 37-41 weeks		
		Q210	Ventricular septal defect					Low birth weight: no		
		Q423	Imperforate anus	Low anal perforation				Karyotype : normal		
R3	Gabapentin	Q210	Ventricular septal defect		Isolated cardiac	At birth	2010-2014	Singleton	None reported	Folic acid, amoxicillin, azithromycin, beclometasone
								Gestational length: 32-36 weeks		
								Low birth weight: yes		
								Karyotype: NA		

R4	Gabapentin	Q210	Ventricular septal defect		Isolated cardiac	NA	2010-2014	Singleton	Maternal epilepsy	Levetiracetam, oxcarbazepine, diazepam
								Gestational length: 32-36 weeks		
								Low birth weight: no		
								Karyotype : normal		
R5	Gabapentin	Q120	Congenital cataract	Anterior congenital cataract	Isolated other	At birth	2010-2014	Multiple birth	Epilepsy, maternal hypothyroidism before pregnancy	Levetiracetam, clobazam, folic acid (5mg) taken in preconception period
								Gestational length: 32-36 weeks		
								Low birth weight: yes		
								Karyotype: NA		
R6	Gabapentin	Q622	Congenital megaloureter	Bilateral megaureter with calicopelviectasia	Isolated renal	Less than 1 week	2010-2014	Singleton	Multiple sclerosis	
								Gestational length: 37-41 weeks		
								Low birth weight: no		
								Karyotype: NA		
R7	Gabapentin	Q900	Trisomy 21, meiotic nondisjunction		Chromosomal (control genetic)	Prenatal diagnosis	2010-2014	Singleton	Hypothyroidism, fibromyalgia	Levothyroxine, oxycodone
								Gestational length: < 28 weeks		
								Low birth weight: NA		
								Karyotype: trisomy 21		
R8	Gabapentin	Q5011		Two ovarial cyste	Isolated other			Singleton		

			Developmental ovarian cyst			Prenatal diagnosis	2015-2020	Gestational length: 32-36 weeks	Allergic contact dermatitis due to metals	Oxycodone, diazepam
								Low birth weight: no		
				<i>Small umbilical hernia</i>				Karyotype: NA		
R9	Gabapentin	Q541	Hypospadias, penile	Hopospasias peneana (ara ventral)	Isolated other	At birth	2015-2020	Singleton	None reported	Alprazolam, chlorpromazine, fosfomycin, diazepam
								Gestational length: 32-36 weeks		
								Low birth weight: yes		
								Karyotype: NA		
R10	Gabapentin	Q909	Down syndrome,		Chromosomal (control genetic)	Prenatal diagnosis	2015-2020	Singleton	None reported	Macrogol, povidone-iodine, methylprednisolone, carbon dioxide producing drugs, budesonide, carbohydrates
								Gestational length: < 28 weeks		
								Low birth weight: Na		
								Karyotype: NA		
R11	Gabapentin	Q210	Ventricular septal defect	VSD small muscular	Isolated cardiac	Over 12 months	2015-2020	Singleton	Multiple sclerosis	
								Gestational length: 37-41 weeks		
								Low birth weight: no		
								Karyotype: NA		
R12	Gabapentin	Q6909	Accessory finger		Isolated other	At birth	2015-2020	Singleton	None reported	
								Gestational length: 37-41 weeks		
								Low birth weight : no		
								Karyotype: NA		

R13	Gabapentin	Q764	Hemivertebra		Isolated cardiac	At birth	2015-2020	Singleton	Anxiety disorder, anogenital (venereal) warts, heavy maternal smoking	Quetiapine, aripiprazole, diazepam, methadone
								Gestational length: 37-41 weeks		
		Q2111	Patent or persistent foramen ovale					Low birth weight: yes		
		Q210	Ventricular septal defect					Karyotype: NA		
R14	Gabapentin	Q701	Webbed fingers	Syndactyly (acrosyndactyly) fingers 3 and 4 right hand with fusion of the single distal phalanx	Isolated other	At birth	2015-2020	Singleton	Anxiety disorder, Hypothyroidism, previous heroin addiction	Diazepam
								Gestational length: 37-41 weeks		
								Low birth weight no		
								Karyotype: NA		
R15	Pregabalin	Q203	Discordant ventriculoarterial connection	Complex heart defect	Isolated cardiac	Prenatal diagnosis	2010-2014	Singleton	Unspecified disorder of psychological development, Other chronic pain	Ibuprofen, anesthetics local, diclofenac, omeprazole, venlafaxine
								Gestational length: 37-41 weeks		
		Q2104	Ventricular septal defect	Subaortal VSD				Low birth weight: no		
		Q221	Congenital pulmonary valve stenosis	PVS critical, almost atresia				Karyotype : No deletion 22q11		

R16	Pregabalin	Q040-	Congenital malformations of corpus callosum	Dysgenesis	Isolated other	Prenatal diagnosis	2010-2014	Singleton	Multiple sclerosis	Interferon beta-1a, lormetazepam, benzodiazepine derivatives
								Gestational length: 37-41 weeks		
								Low birth weight: no		
								Karyotype: NA		
R17	Pregabalin	Q210	Ventricular septal defect		Isolated cardiac	At birth	2010-2014	Singleton	None reported	Sertraline
								Gestational length: 37-41 weeks		
								Low birth weight: no		
								Karyotype: NA		
R18	Pregabalin	Q379	Unspecified cleft palate with unilateral cleft lip		Isolated other	NA	2010-2014	Singleton	None reported	Soft paraffin and fat products, phloroglucinol, paracetamol, tramadol, cortivazol, diclofenac, pantoprazole, ketoprofen, metopimazine, racecadotril, diosmectite, econazole, zolpidem, niflumic acid, carbon dioxide producing drugs, tetrazepam
								Gestational length: 37-41 weeks		
								Low birth weight :no		
								Karyotype: NA		
R19	Pregabalin	Q211	Atrial septal defect		Isolated cardiac	NA	2010-2014	Singleton	None reported	Insulin aspart, insulin (human),calcium folinate, oxomemazine, pseudoephedrine,
								Gestational length: 32-36 weeks		
								Low birth weight: no		

								Karyotype: NA		combinations, tropicamide, hydroxyzine, desloratadine, chlorhexidine, phenylephrine, diclofenac, metoclopramide, acetyllecine, tetrazepam, omeprazole, paracetamol, lidocaine, betahistine, ketoprofen, norfloxacin, mometasone
R20	Pregabalin	Q210	Ventricular septal defect	Small VSD	Isolated cardiac	1-4 weeks	2010-2014	Singleton	Depressive episode, threatened abortion	Ciprofloxacin, salbutamol, cloxacillin, streptokinase, dexketoprofen, mupirocin, omeprazole, zolpidem
								Gestational length: 32-36 weeks		
		Q256	Stenosis of pulmonary artery	Mild pulmonary stenosis				Low birth weight: yes		
		Q2111		Patent foramen ovale				Karyotype: 46 xx		
R21	Pregabalin	Q2519	Coarctation of aorta		Isolated cardiac	Prenatal diagnosis	2010-2014	Singleton	None reported	Levothyroxine
		Q250	Patent ductus arteriosus	Ductus 5mm				Gestational length: 37-41 weeks		
		Q2111	Patent or persistent foramen ovale	VSD, patent foramen ovale 3mm				Low birth weight: no		
								Karyotype: NA		
R22	Pregabalin	Q758						Singleton		Paracetamol

			Other specified congenital malformations of skull and face bones	Dysostose maxillo nasale	Genetic syndrome, skeletal dysplasia and monogenic disorder (control genetic)	Prenatal diagnosis	2015-2020	Gestational length: 37-41 weeks	Excessive vomiting in pregnancy	
								Low birth weight: yes		
		Q773	Chondrodysplasia punctata	Brachytelephalangal chondrodysplasia punctata				Karyotype: NA		
R23	Pregabalin	Q038	Other congenital hydrocephalus	Suprasensory hydrocephalus with lateral left ventricle	Isolated other	NA	2015-2020	Singleton	B-cell lymphoma	
								Gestational length: 37-41 weeks		
								Low birth weight: no		
								Karyotype: NA		
R24	Pregabalin	Q660	Talipes equinovarus	Left clubfoot	Isolated other	NA	2015-2020	Singleton	None reported	Paracetamol
								Gestational length: 37-41 weeks		
								Low birth weight: no		
								Karyotype: NA		
R25	Pregabalin	Q210	Ventricular septal defect		Isolated cardiac	Prenatal diagnosis	2015-2020	Multiple birth	Mental disorders and diseases of the nervous system	Zopiclone, mirtazapine, lorazepam
								Gestational length: 28-31 weeks		
								Low birth weight: yes		
								Karyotype: NA		
R26	Pregabalin	Q621			Isolated renal	At birth		Singleton	None reported	

			Atresia and stenosis of ureter	Unspecified obstructive defect of the pelvis of the kidney and ureter			2015-2020	Gestational length: 37-41 weeks		Progesterone, levothyroxine
								Low birth weight: no		
								Karyotype: NA		
R27	Pregabalin	Q871	Lenz-majewski syndrome		Genetic syndrome, skeletal dysplasia and monogenic disorder (control genetic)	At birth	2015-2020	Singleton	None reported	Mepyramine theophyllinacetate, megestrol, ketoconazole, fluconazole, fenticonazole, metamizole, doxycycline, omeprazole, ibuprofen, enalapril, diazepam, simvastatin, folic acid
								Gestational length: 37-41 weeks		
								Low birth weight: yes		
								Karyotype normal		
R28	Pregabalin	Q211	Atrial septal defect		Isolated cardiac	At birth	2015-2020	Multiple birth	Fibromyalgia, allergy to analgesic agent, urinary tract infection	Celecoxib, codeine and ibuprofen
								Gestational length: 32-36 weeks		
								Low birth weight: yes		
								Karyotype: NA		
R29	Pregabalin	Q203	Transposition of great vessels	Cardiopathy with intact septum	Isolated cardiac	Prenatal diagnosis	2015-2020	Singleton	Hypertension, migraine, pre-eclampsia,	Potassium clorazepate, enalapril, sertraline, duloxetine, fluoxetine, methyl dopa
		Q210	Ventricular septal defect					Gestational length: 37-41 weeks		

		Q2111	Patent or persistent foramen ovale					Low birth weight: no		
		Q250	Patent ductus arteriosus					Karyotype: NA		
R30	Pregabalin	Q540	Hypospadias, balanic	Hypospadias, glandular	Isolated other	At birth	2015-2020	Singleton	Asthma, infection of urinary tract in pregnancy, Other chronic pain	Nitrofurantoin, meclozine
								Gestational length: 37-41 weeks		
								Low birth weight: no		
								Karyotype : Normal		
R31	Pregabalin	Q700	Fused fingers	Syndactyly 4 and 5 finger right hand	Isolated other	At birth	2015-2020	Singleton	None reported	Dexketoprofen
								Gestational length: 37-41 weeks		
								Low birth weight: no		
								Karyotype: NA		
R32	Pregabalin	Q210	Ventricular septal defect	Non-restrictive muscular VSD	Multiple congenital anomalies	At birth	2015-2020	Singleton	Hypothyroidism, Gestational diabetes	Amoxicillin and beta-lactamase inhibitor, azithromycin, ibuprofen, rizatriptan, cyclobenzaprine, paracetamol,
								Gestational length: 37-41 weeks		
		Q549	Hypospadias, unspecified					Low birth weight: no		
		Q531	Undescended testicle, unilateral	Left cryptorchidism				Karyotype: NA		

										levothyroxine, amoxicillin
R33	Pregabalin	Q6210	Atresia and stenosis of ureter	Right pyelo ureteral junction syndrome	Isolated renal	Prenatal diagnosis	2015-2020	Singleton	Guillain-Barré syndrome	Lidocaine, paracetamol, amitriptyline
								Gestational length: 37-41 weeks		
								Low birth weight: no		
								Karyotype: NA		
R34	Pregabalin	Q410	Congenital absence, atresia and stenosis of duodenum	Estenosis (atresia) duodenal	Isolated other	Prenatal diagnosis	2015-2020	Singleton	Obesity	Dexketoprofen, naproxen, domperidone,
								Gestational length: 36-36 weeks		
								Low birth weight: yes		
		Q2111	Patent or persistent foramen ovale	PFO 1,8mm				Karyotype: NA		
R35	Pregabalin	Q210	Ventricular septal defect	VSD of the middle third cc i-d	Isolated cardiac	Less than 1 week	2015-2020	Multiple pregnancy	Gestational Diabetes	Ibuprofen, omeprazole, fenticonazole, paracetamol, ranitidine
								Gestational length: 37-41 weeks		
								Low birth weight: no		
								Karyotype: NA		
R36	Pregabalin	Q379	Unspecified cleft palate with unilateral cleft lip		Genetic syndrome, skeletal dysplasia and monogenic disorder	NA	2015-2020	Singleton	None reported	Phloroglucinol, metoclopramide, paracetamol
								Gestational length: 37-41 weeks		
								Low birth weight no		

		Q870	Congenital malformation syndromes predominantly affecting facial appearance		(control genetic)			Karyotype: NA		
R37	Pregabalin	Q620	Congenital hydronephrosis		Isolated renal	Prenatal diagnosis	2015-2020	Singleton Gestational length: 32-36 weeks Low birth weight: no Karyotype: NA	None reported	Ciclopirox, econazole, promestriene, terbutaline, ferrous ascorbate

Footnote : **NA**: not available

